Why Nutrition of the Preterm Matters – Long-Term Consequences of Adverse Early Nutrition and Growth

Presented by
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Presented at
Miami Neonatology 2016 – 40th International Conference
November 5th-8th, 2016

This activity is supported by an educational grant from
Mead Johnson Nutrition.

Disclosure

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosure has been made:

William W. Hay, Jr. MD

One time Consultant: Baxter–IV nutrition

Adverse outcomes of under nutrition of preterm infants

- Worse neurodevelopment, poorer cognition, abnormal behavior (Michael Georgieff's presentation)
- Shorter stature, smaller brains, increased obesity and dysglycemia (this presentation; Michael's; and Neena Modi's)

Adverse outcomes of over nutrition of preterm infants

- Obesity, insulin resistance, glucose intolerance, type 2 diabetes (Neena Modi's presentation and this presentation)
- Cardiovascular disorders (hypertension, myocardial infarction, stroke (Neena Modi's presentation)

Beneficial outcomes of feeding preterm infants human milk

All of us!

How does nutrition affect development?

The Fundamental Mechanism

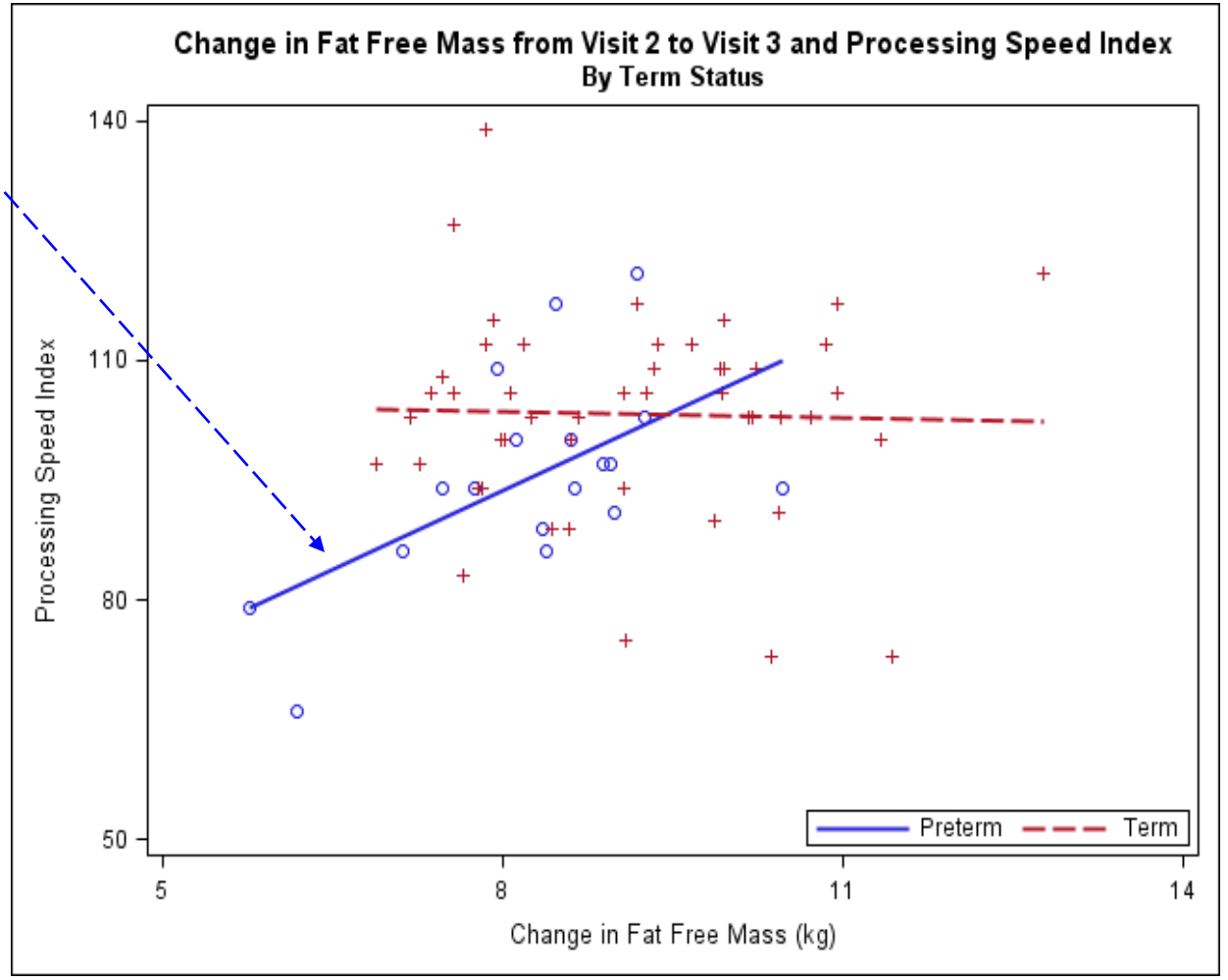
"Programming"

A stimulus or insult, when applied at a *critical or sensitive stage* in development [*and of sufficient magnitude, duration, and developmental plasticity*], may result in a lasting, even lifelong effect on the structure or function *[or both]* of the organism.

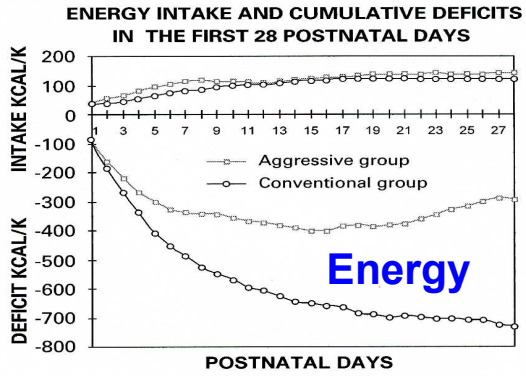
Modified from Alan Lucas, CIBA Symp. 156, 1991

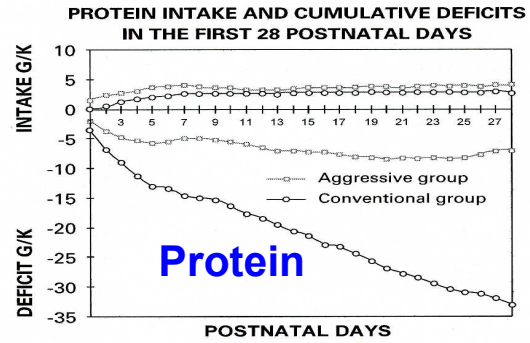
Critical developmental stage is fundamental—eg, body composition changes—Fat Free Mass gain—associated with neurodevelopment in preterm infants but not those born at term.

- **FFM gains in preterm infants** (<36 weeks) from 4 months CA to 4 years were positively associated with cognition at 4 years of age.
- These associations were not seen in term infants or for Fat Mass changes.



Scheurer JM, et al. Preterm Infants' Fat-Free Mass Accretion Impacts Preschool Cognition [abstract]. E-PAS 2015:3130.6.





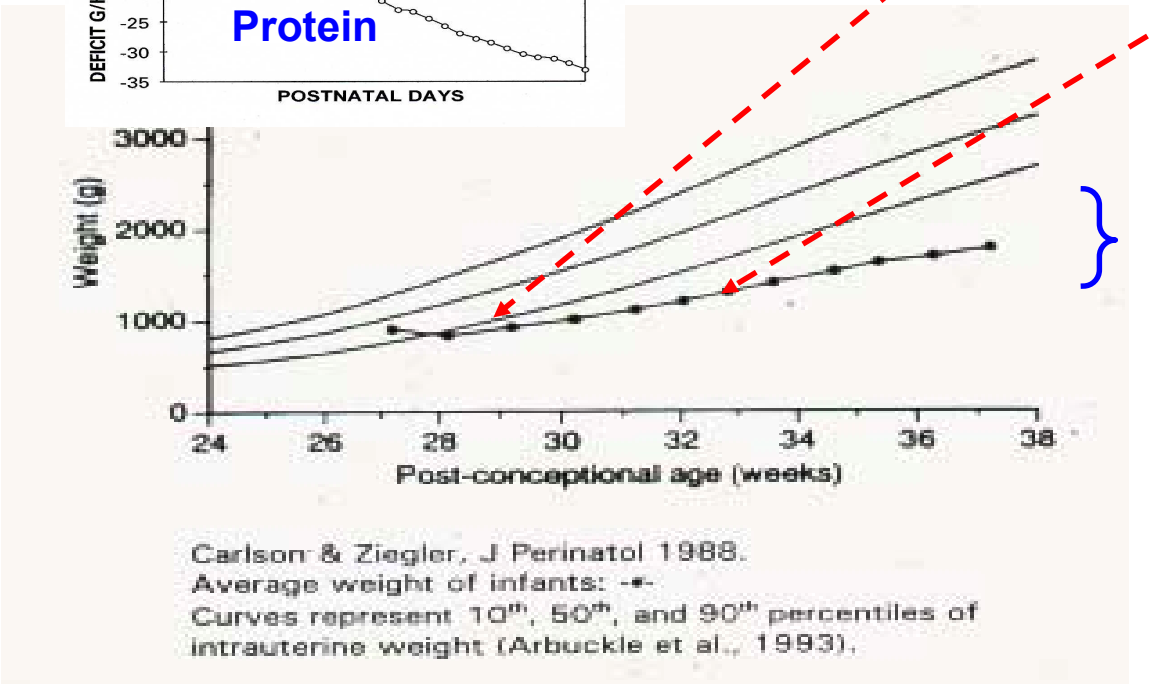
A principal nutritional disorder of preterm infants is

under nutrition.

Most preterm infants fail to grow well after birth, usually for many days,

they don't keep up with intra uterine growth,

and thus they end up growth restricted by term.



Critical stage—preterm
Under nutrition
?? consequences

Upper: Dinerstein A, et al. *J Perinatol.* 2006;26:436-442. With permission Macmillan Publishers Ltd: *J Perinatol.* 26:436-442, copyright 2006.
Lower: Carlson SJ, and Ziegler EE. *J. Perinatol.* 18:252-258, 1998. With permission.

Why are Preterm VLBW Infants not fed enough to grow as the fetus does?

1. Delayed start to providing nutrients, eg, low or no IV amino acids on day 1 (to sometimes several days after birth); enteral feedings held, sometimes for days;

2. Slow advances of nutrient supplies, eg, IV amino acid infusion rates of < 3 g/kg/d; slow advances of IV amino acids after starting; slow advances of enteral feeds;

3. Dilute nutritional mixes, eg, breast milk (mother's own or banked); insufficient essential amino acids in TPN mixes.

These are the facts.

But these are the "Reasons"!

(aka "Excuses")

1. abdominal distension—"feeding intolerance," fear of NEC
2. green gastric aspirates—"feeding intolerance," fear of NEC
3. UA and/or UV catheters—fear of gut ischemia, and thus NEC
4. GER—fear of apnea (actually, it probably is the other way around)
5. tachypnea—fear of aspiration
6. heart murmurs—fear of PDA and gut ischemia—and NEC
7. PDAs—fear of gut ischemia—and NEC
8. indomethacin—fear of gut ischemia—and NEC
9. high BUN—fear of urea poisoning and amino acid toxicity
10. high bilirubin—fear of FFA displacing bilirubin from albumin
11. high WBC/CRP—fear of decreased metabolism, proteolysis
12. skin rashes—fear of allergies
13. hyperglycemia—fear of poor metabolism (though reducing GIR at least has a rational basis)
14. hypothermia—fear of sepsis
15. hyperthermia—fear of sepsis

And more—

16. hypo- or hyperkalemia—poor gut function, bad IV nutrient mix
17. hypo- or hypernatremia—bad IV nutrient mix, dehydrated
18. thrombotic episodes—need to use heparin, reduce IV rate
19. polycythemia—risk of clots and gut ischemia and NEC
20. SpO_2 values are low—can't metabolize nutrients
21. on catecholamines—fear of gut ischemia, NEC, hyperglycemia
22. Anemia—fear of gut ischemia
23. Transfusions—risks of NEC, TRIM (transfusion related immunomodulation)

And more! (and my editorial responses on rounds)

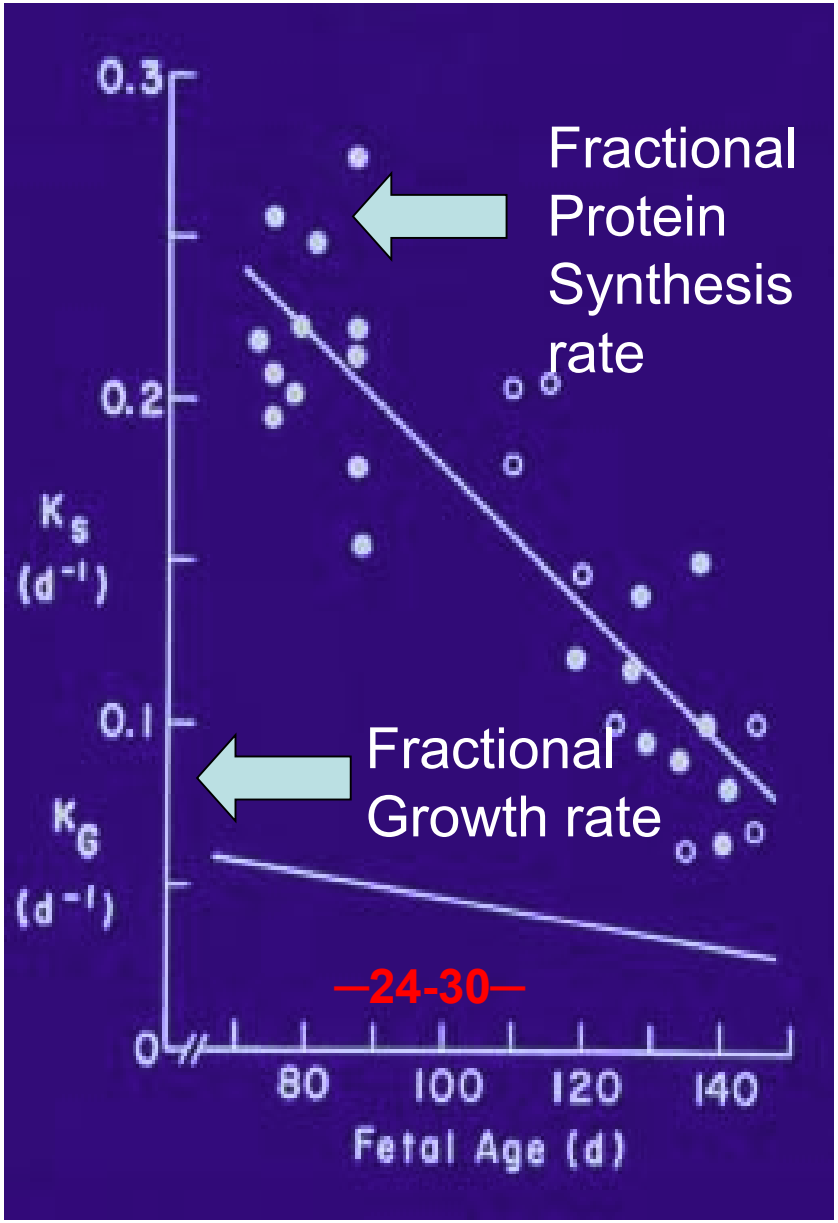
24. on a ventilator—how does this reduce digestion and nutrient absorption and anabolism?
25. low energy expenditure—this one baffles me; of course it's low if the baby is under-nourished!
26. might need surgery—so they should be starved first?
27. "Just doesn't look good" — I have no response to this one!

And more—

28. Mother couldn't be here so we held the feeding for her to give (yea Mom, but poor baby!)
29. Intermittent Hypoxic Episodes (these get better with starvation??)
30. We wanted "fasting" electrolyte values in the morning (Really! ??).
31. We wanted to be sure the baby was stable (well, sure, and starved, too).
32. "The other attending" doesn't like to advance feeds very fast (always a scapegoat around—the ubiquitous, infamous "other attending") .
33. IUGR/SGA infant—dangerous to feed them, especially if they had abnormal Doppler velocimetry (why is starvation better?).
34. IDM—wanted to stabilize the blood glucose with IV dextrose first (I can always do better by enteral feeding of lactose).
35. Intermittent apnea episodes (this is fixed by starvation?).
36. We're going to transport the baby to--- (So you starve a baby first?).
37. The baby was cold (starve a cold, feed a fever?).
38. Amino acid concentrations might be toxic (more commonly, too low)

The reasons ("excuses") seem never ending. And all of these excuses, justified or not, reduce nutrient intake, which leads to growth failure, and worse neurodevelopmental outcomes.

The primary "under nutrition" disorder is insufficient protein.



Fractional Protein Synthesis and Growth rates are high in the fetus, requiring large weight-specific amino acid uptake rates, especially early in med- to late gestation.

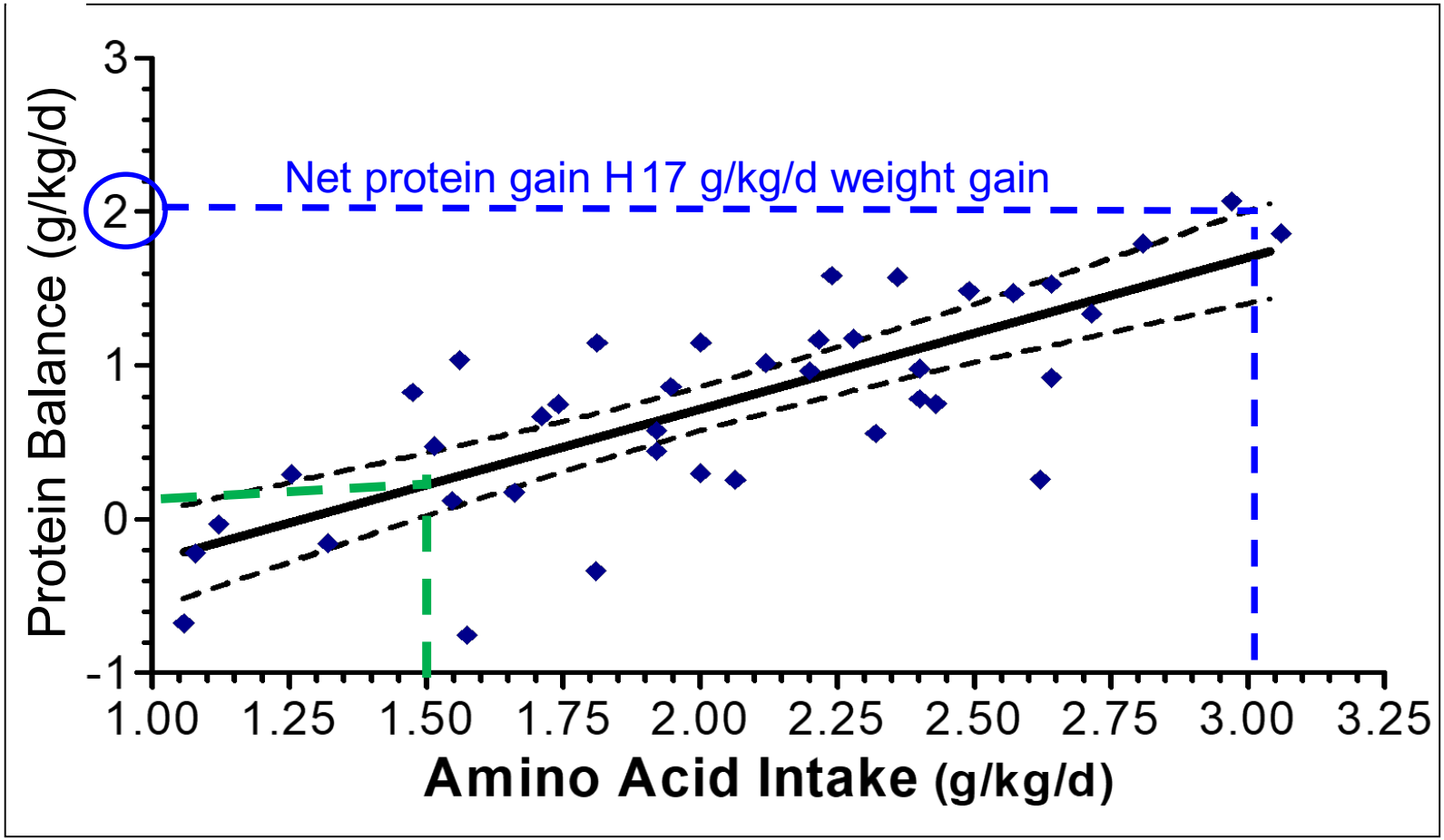
Fetal animal growth data, when scaled to human fetal growth rate, predict fetal amino acid requirements of 3.6-4.8 g/kg/day

Factorial Method (Ziegler)—defines **human** fetal amino acid requirements of 4 g/kg/day

At **24-30** weeks gestation

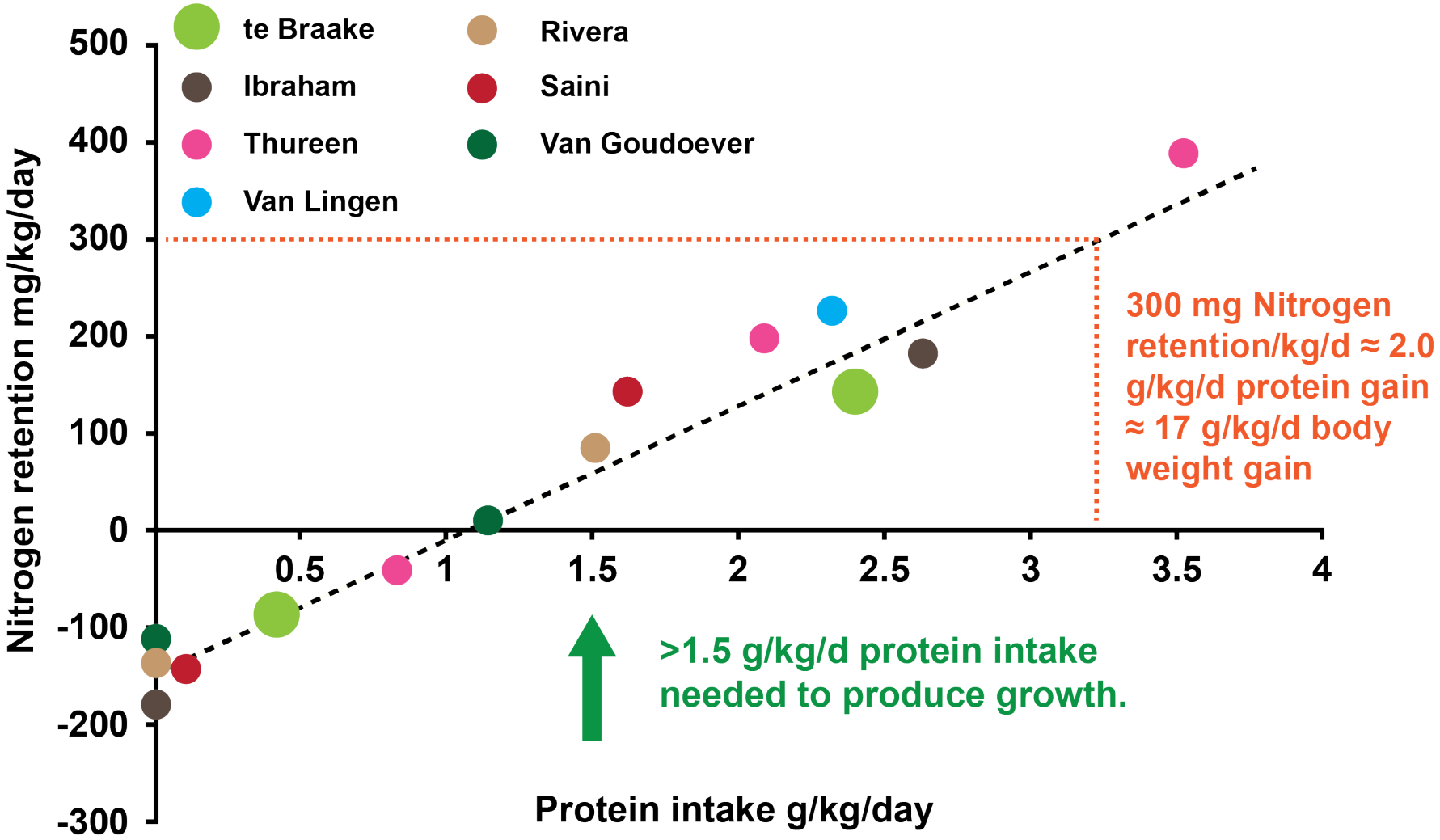
Hay Jr WW, et al. Fetal requirements and placental transfer of nitrogenous compounds. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 4th ed. Philadelphia, PA: Saunders; 2011:585-614.

The good news is that
even right after birth (24-48 hrs), and in unstable infants, there is a direct correlation between amino acid supply and protein balance, through at least 3 g/kg/day.



Thureen PJ, et al. *Pediatr Res*. 2003;53:24–32. With permission.

And this is true across many studies, showing that nitrogen retention (protein balance) is directly and linearly related to protein intake in preterm infants.



Adapted from Embleton ND. *Early Hum Dev.* 83: 831–837, 2007.

In humans, breast feeding and human milk appear to be our best bets.

Breastfeeding, considered dichotomously (yes or no), and the Odds Ratio for Later Obesity

- Obesity in the US affects 35%, of adults (~17% of youth aged 2-19).
- Women that were OW/OB prior to conception carried 60% of all US pregnancies (2013).
- Children born to obese mothers have increased likelihood of childhood obesity.
- Exclusive breastfeeding is protective against elevated obesity risk.

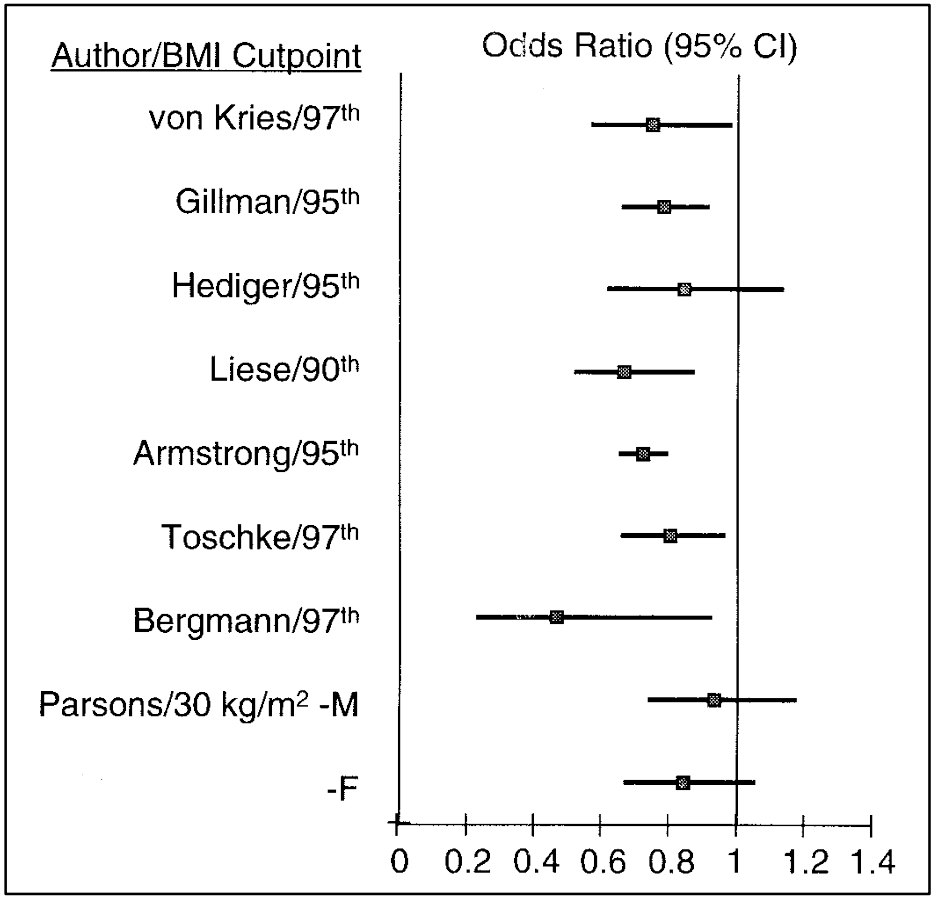
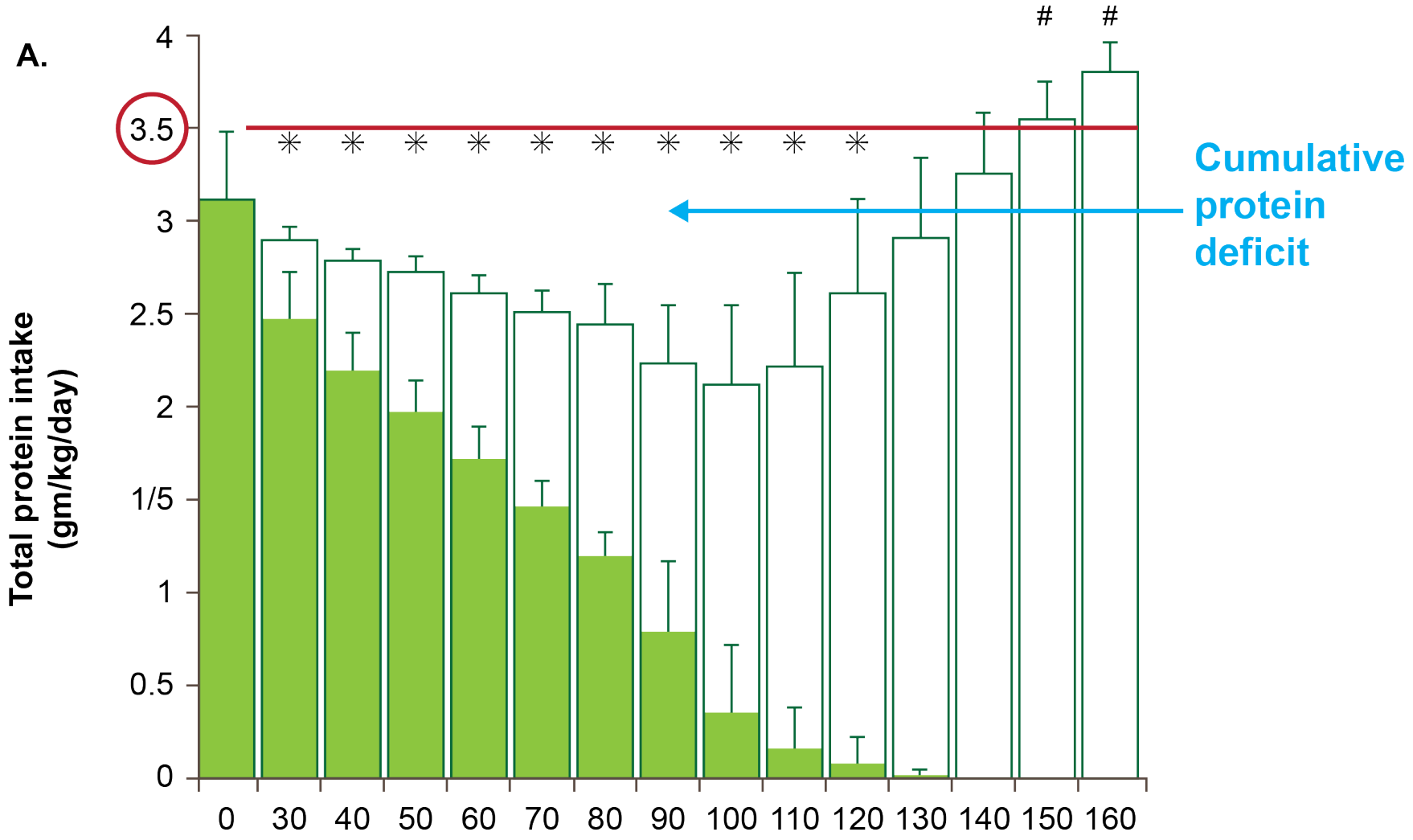


Fig 6. Breastfeeding, considered dichotomously (yes or no), and the OR for later obesity.

Why long enough? Because total protein intake can fail to meet requirements when IV nutrition is weaned ahead of sufficiently increased enteral nutrition.



Miller M, et al. From parenteral to enteral nutrition: A nutrition-based approach for evaluation of postnatal growth failure in preterm infants. *J Parent Ent Nutr.* 2014;38:489-497 (Maimonides Inf Child—New York).

Does it does matter? YES.

First-Week Protein and Energy Intakes are associated with 18-Month Developmental Outcomes in Extremely Low-Birth-Weight Infants

- Protein intake and energy intake during **week 1** each had independent effects on MDI at 18 months
- **Every 1 g/kg/d increase in protein intake associated with 8.2 point increase in MDI at 18 months (both females and males)**
- Every 10 kcal/kg/d increase in energy intake associated with 4.6 point increase in MDI **at 18 months**

Stephens BE, et al. *Pediatrics.* 2009;123:1337–1343

And it can matter for a long time!

First 3 Weeks Protein and Energy Intakes are positively associated with body composition benefits in 20-yr old adults born as very LBW infants (<28 weeks).

- **Every 1 g/kg/d increase in protein intake (starting at low intakes) associated with:**
  - **22.5% higher lean body mass**
  - **22.1% higher resting energy expenditure**
- Similar associations seen with energy and fat, but not carbohydrate.
- **Energy and fat intakes were most positively associated with BMI and % body fat.**

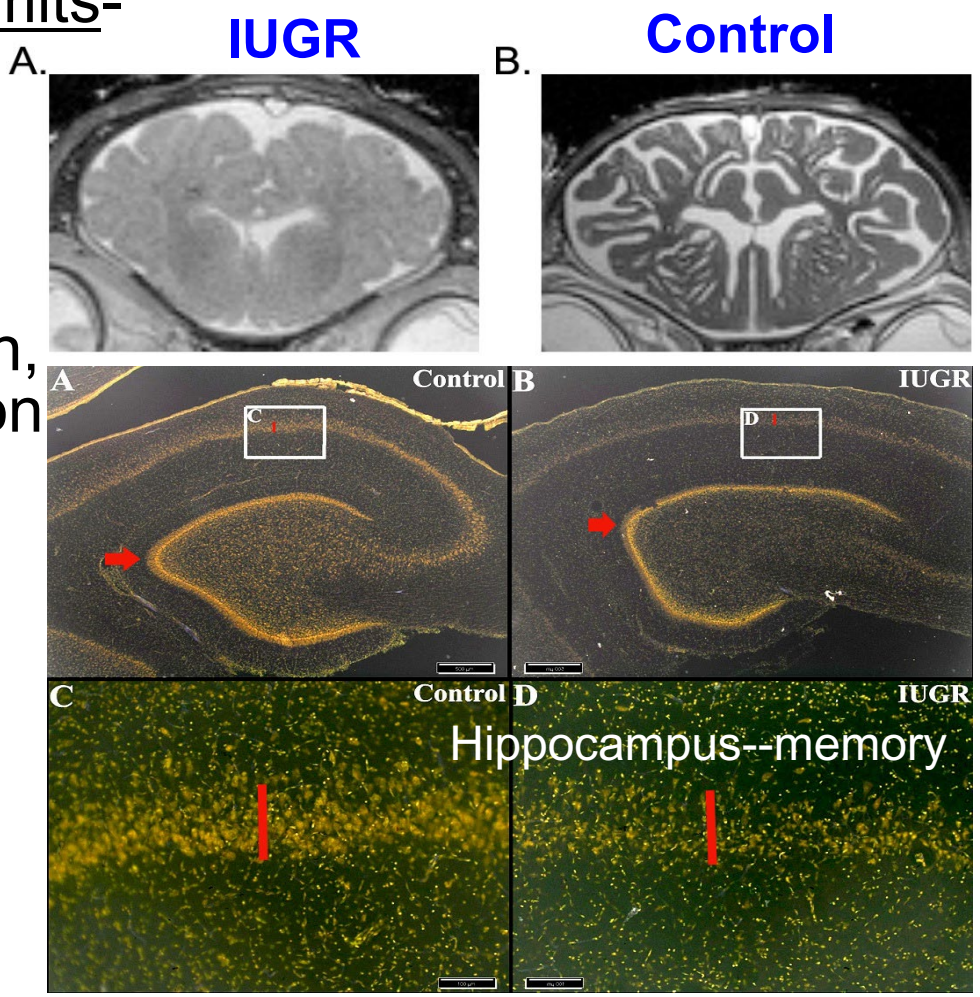
Matinolli H-M, et al. *J Nutr.* 2015;145:2084-2091--Finland

Under Nutrition: Brain growth failure

Under nutrition, principally of protein, at critical stages of development permanently limits-

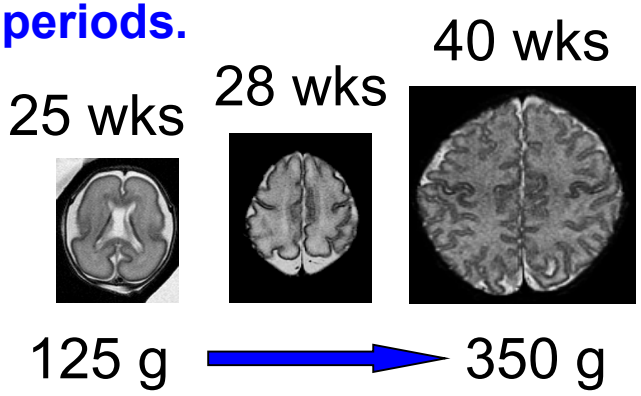
Structural growth
- neuronal number;
- axonal length;
- dendritic number,
  - spine formation,
  - and arborization
- synapse formation

Functional development
- cognitive functions (learning, **memory**), and interactive behavior and mental health disorders.



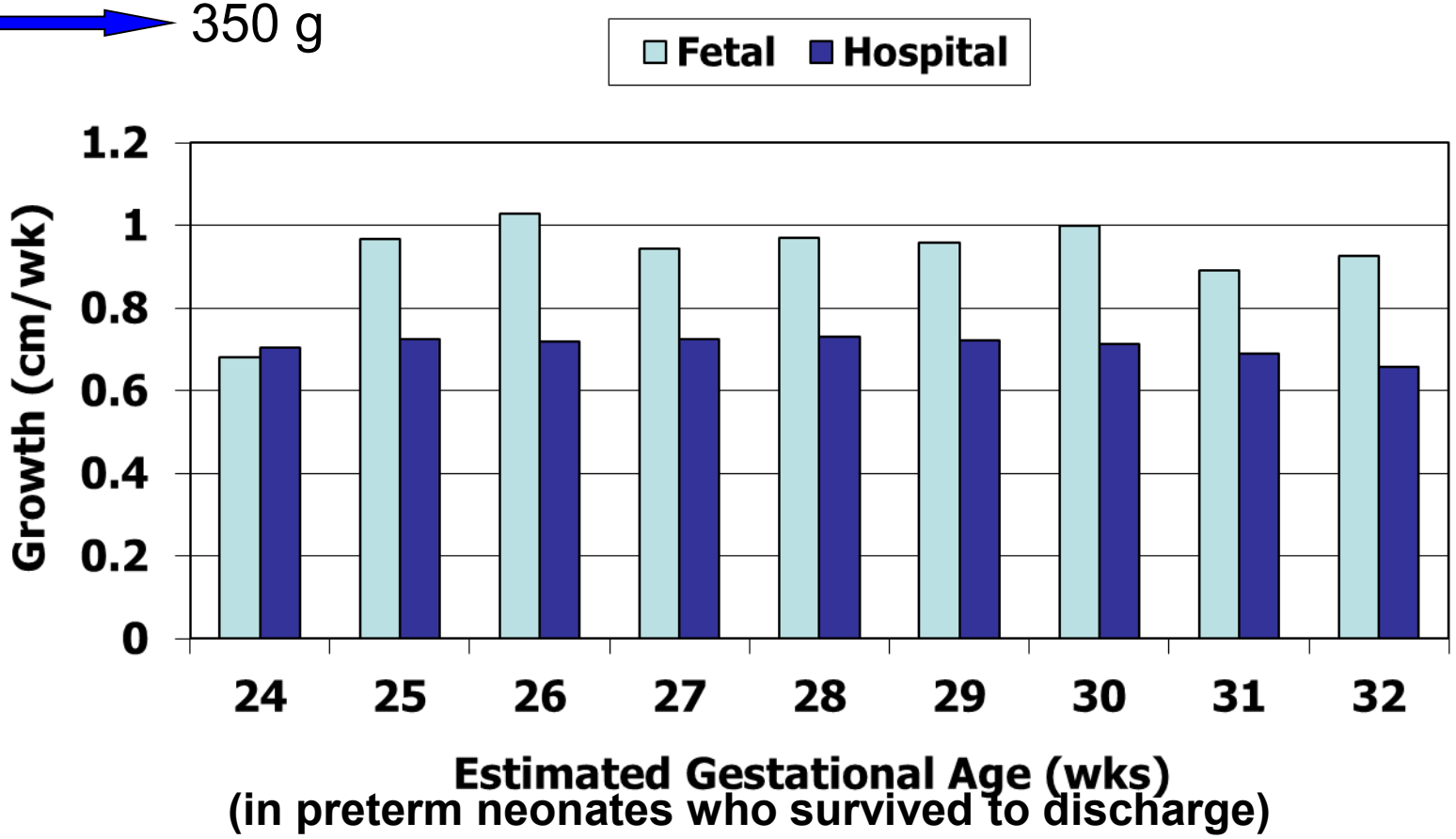
Smart JL. Vulnerability of developing brain to undernutrition. *Ups J Med Sci.* 1990; 48 [suppl]: 21–41.

Huge increase in brain growth at critical developmental periods.



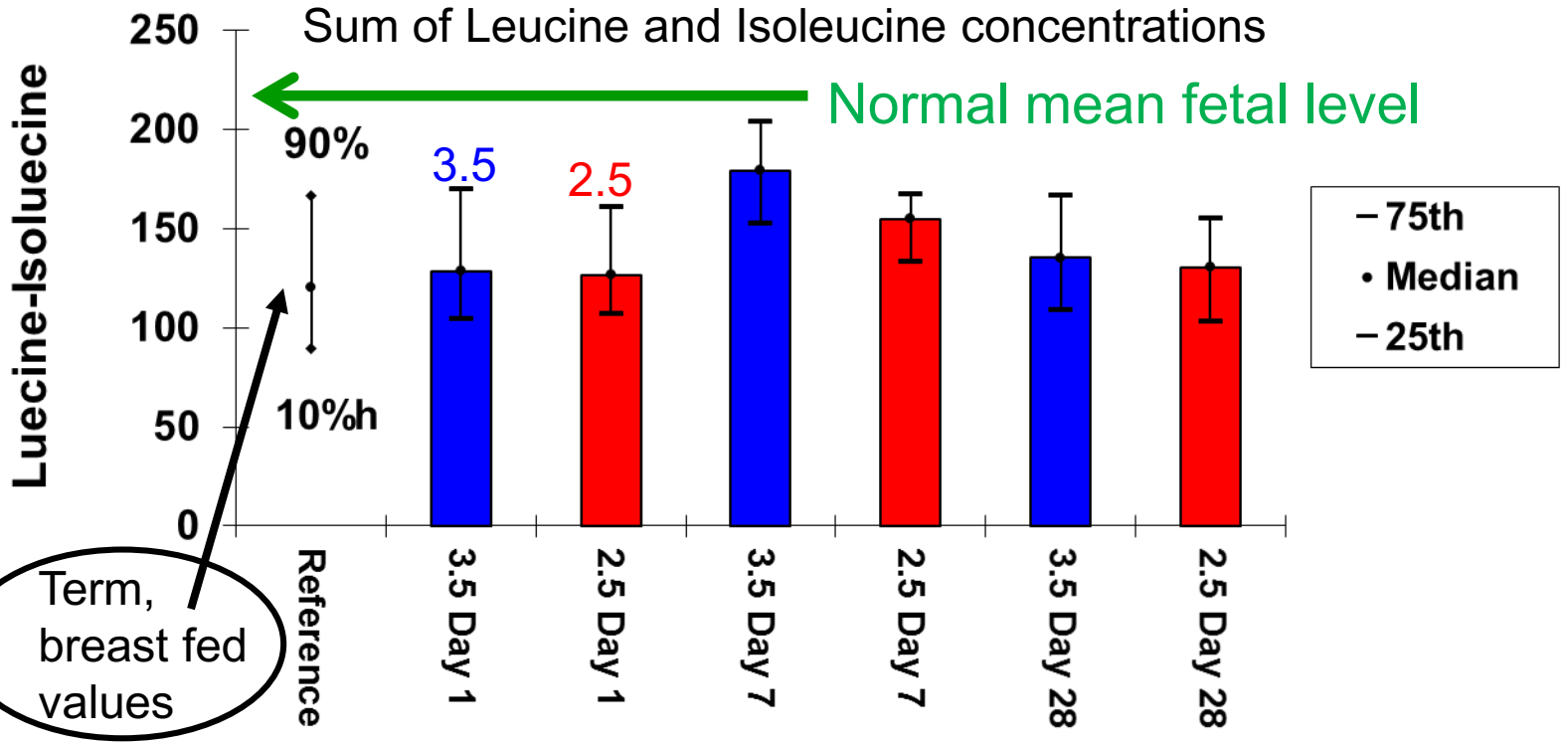
But those are animal studies.

How are we doing with preterm infants' head growth?



Perhaps inadequate essential amino acids?

Pediatrix Study

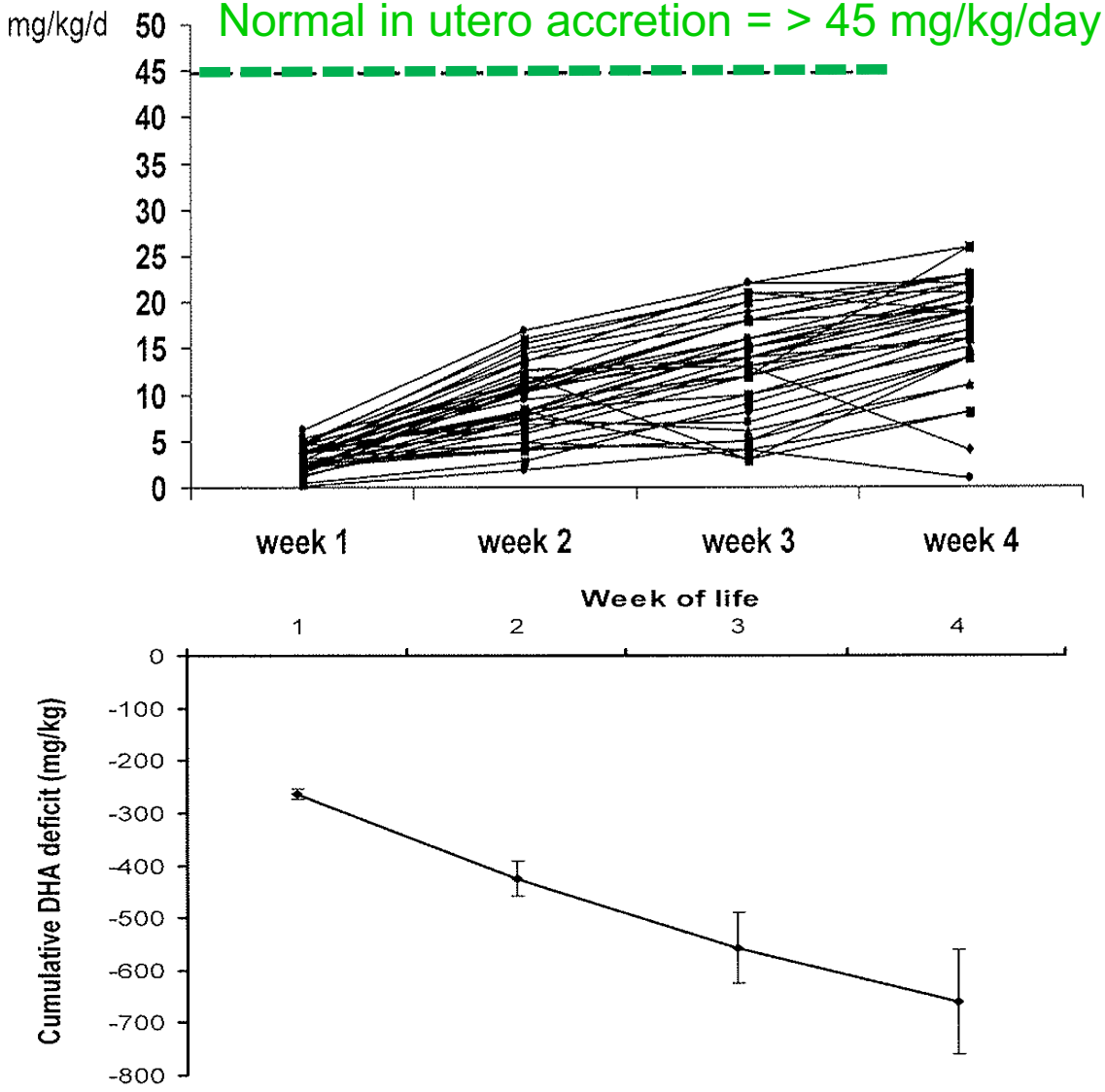


Thus, these infants got only 2/3 of required amounts of *at least* 2 essential amino acids

(unless you are trying to grow at term rates!).

Figure courtesy of Clark RH, Chace DH, Spitzer AR; Pediatrix Amino Acid Study Group.

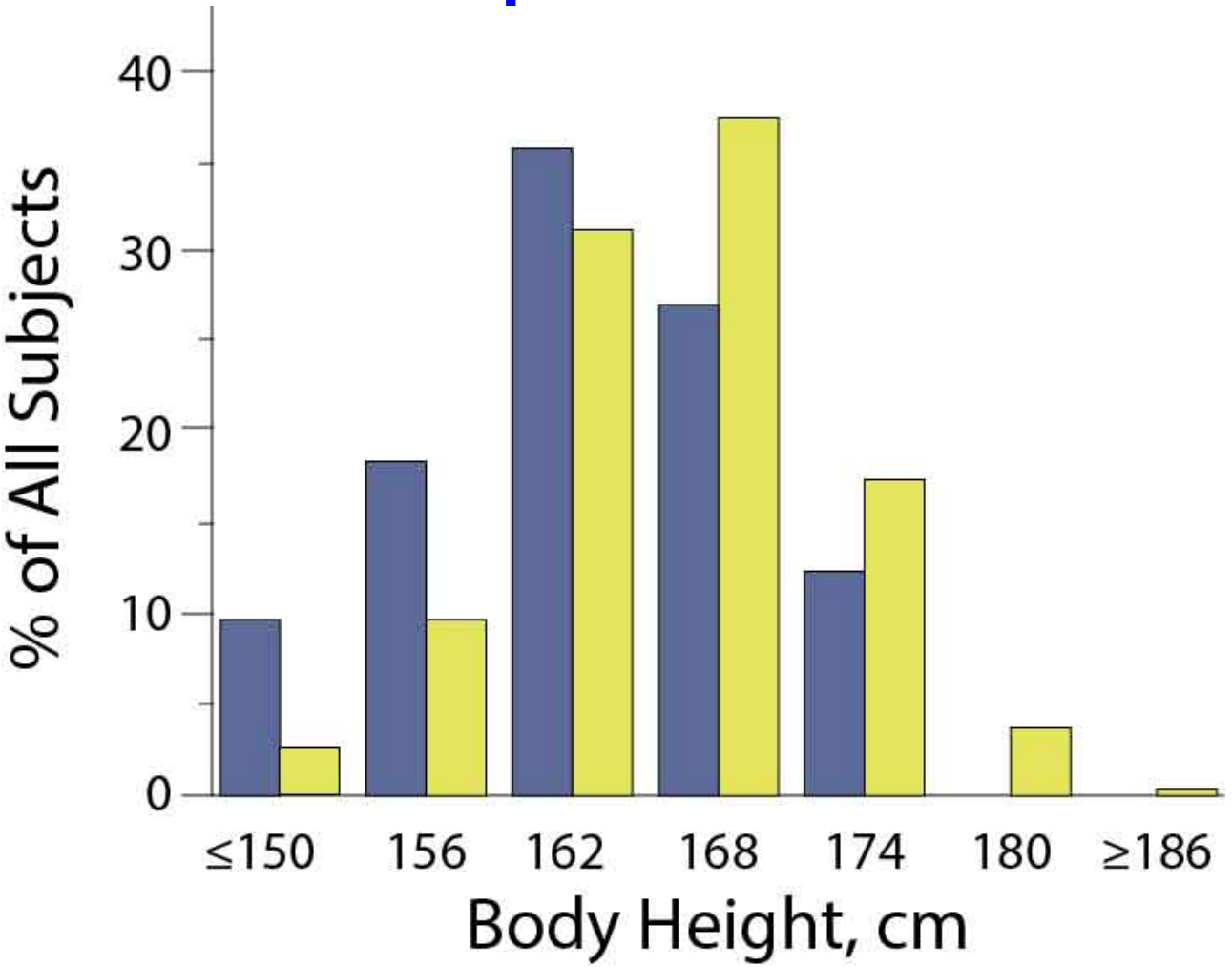
Or structural developments linked to neuronal function and later cognition--??



Postnatal DHA deficiency is an inevitable consequence of current recommendations and practices for feeding milk, milk supplements, and formulas in preterm infants, leading to cumulative increases in DHA deficits.

So far, though, no evidence that this leads to worse long term neurodevelopmental outcomes.

Long term outcome—short stature, programmed by protein deficiency in the fetus and/or preterm infant



Distribution of height at age 17 years in 34 girls born small for gestational age (blue bars) and their peers who were appropriate for gestational age (yellow bars).

Adapted from Paz I, et al. *Am J Dis Child*. 1993;147:337-9.

Long term outcome—height/length (stature) directly related to improved neurodevelopment.

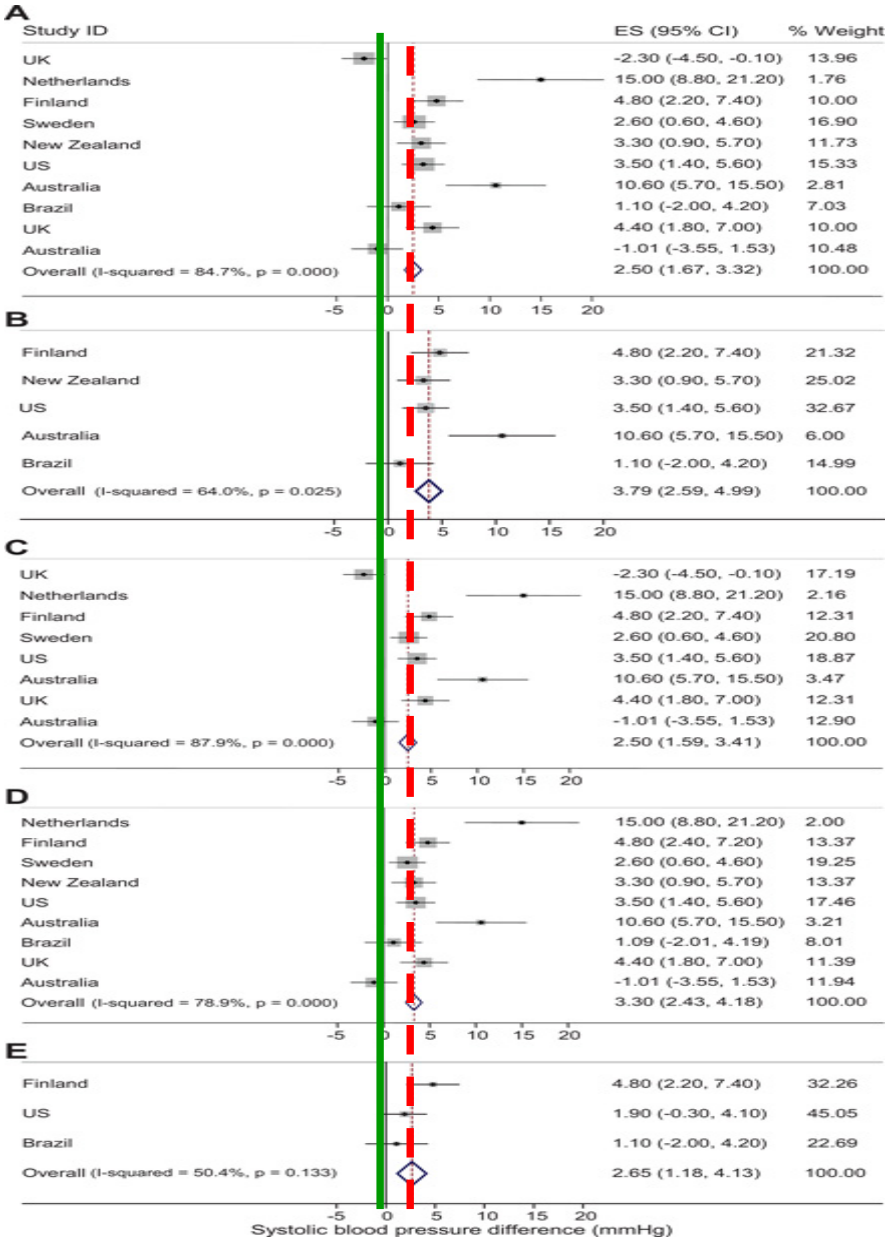
- Infants born **<33 weeks** (mean=30 weeks)
- **Linear growth** from *term to 4 months* CGA associated with **higher motor scores at 18 months**

- Infants born **≤37 weeks** and LBW (mean=33 weeks and 1800 grams)
- Increased **linear growth** from *term to 4 months* CGA, **decreased odds of IQ <85 at 8 and 18 years**

- **<1250g AGA and SGA infants**
- **Linear growth** from *birth to 2 years* of age **positively correlated with PDI** and **negatively with CP**

Belfort et al. *Pediatrics.* 2011;128:e899–906.
Belfort et al. *J Pediatr.* 2013;163(6):1564–9.e2.
Latal-Hajnal et al. *J Pediatr.* 2003;143(2):163-7.

Long term outcome—preterm birth and undernourishment associated with cardiovascular problems.



Nearly all follow-up studies show increased systolic blood pressure in children and adults who were born very preterm

vs those born at term,

but the difference is small—2-3 mmHg.

Clinical significance ?

A nutritional disorder ?

De Jong et al. Systematic Review and Meta-Analysis of Preterm Birth and Later Systolic Blood Pressure. *Hypertension.* 2012;59:226-234.

Preterm birth, but more common in IUGR infants, leads to **impaired nephrogenesis**.

- Protein deficiency?—true in controlled animal studies (Woods)
- Nephrotoxic medications—no real studies of the impact of furosemide, one of the most commonly used drugs in preemies.
- Hypoxic and ischemic injuries to kidney, and development of transient (but often treated) hypertension, cause(s) uncertain.

Associated with hypertension, but why, when nephrectomy later in life does not always produce hypertension?

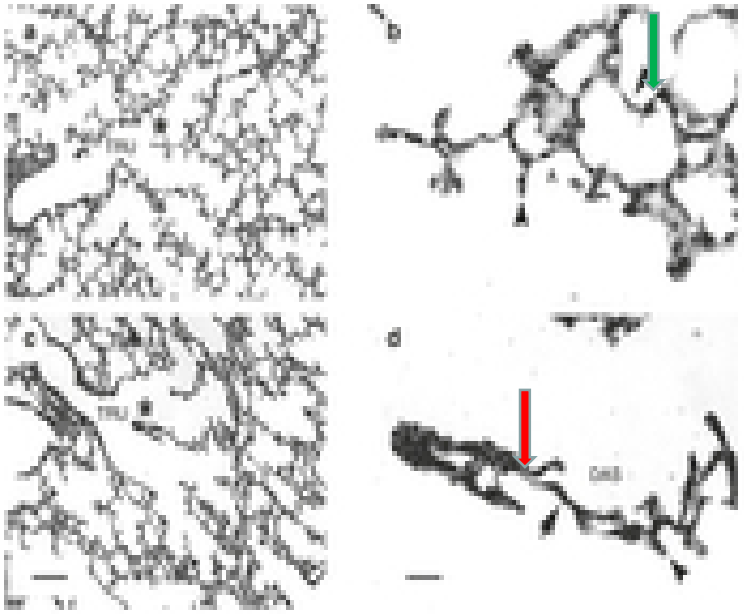
Thornburg KL. The programming of cardiovascular disease. *J Dev Orig Health Dis.* 2015;6:366-376.

Long term outcome—underdeveloped lungs

Restricted nutrition contributes to impaired alveolar formation during the evolution of BPD in chronically ventilated preterm lambs.

Control lung alveolar morphology

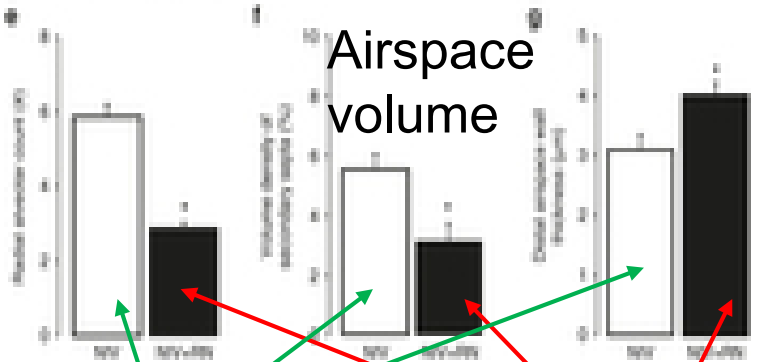
Restricted nutrition lung alveolar morphology



Control—thinner DAS walls

Distal airspace (**DAS**) walls

Nutrient Restricted—thicker DAS walls



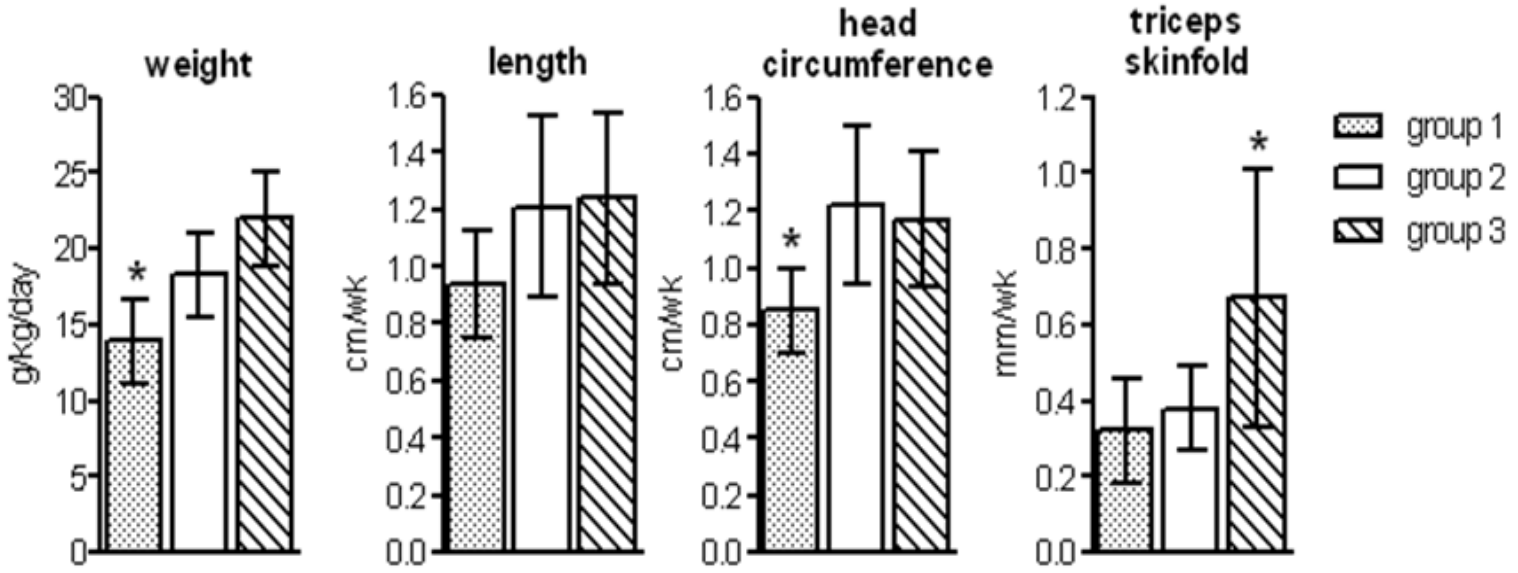
? Relation to asthma
? Reduced adult lung function

The second most common nutritional disorder of preterm infants is Over Nutrition (energy!): The result--

- High calorie to protein ratio diet will lead to fatter, shorter, less muscular infants, and perhaps to higher blood pressure and even neurological deficits.
- Overfeeding infants leads to adult obesity, regardless of their fetal development of fat mass
- And other problems—not enough time to review.
  - Overfeeding rat pups during suckling leads to adult hypercholesterolemia and hyperinsulinemia
  - High carbohydrate diet following weaning further increases enzymes that produce cholesterol and fat

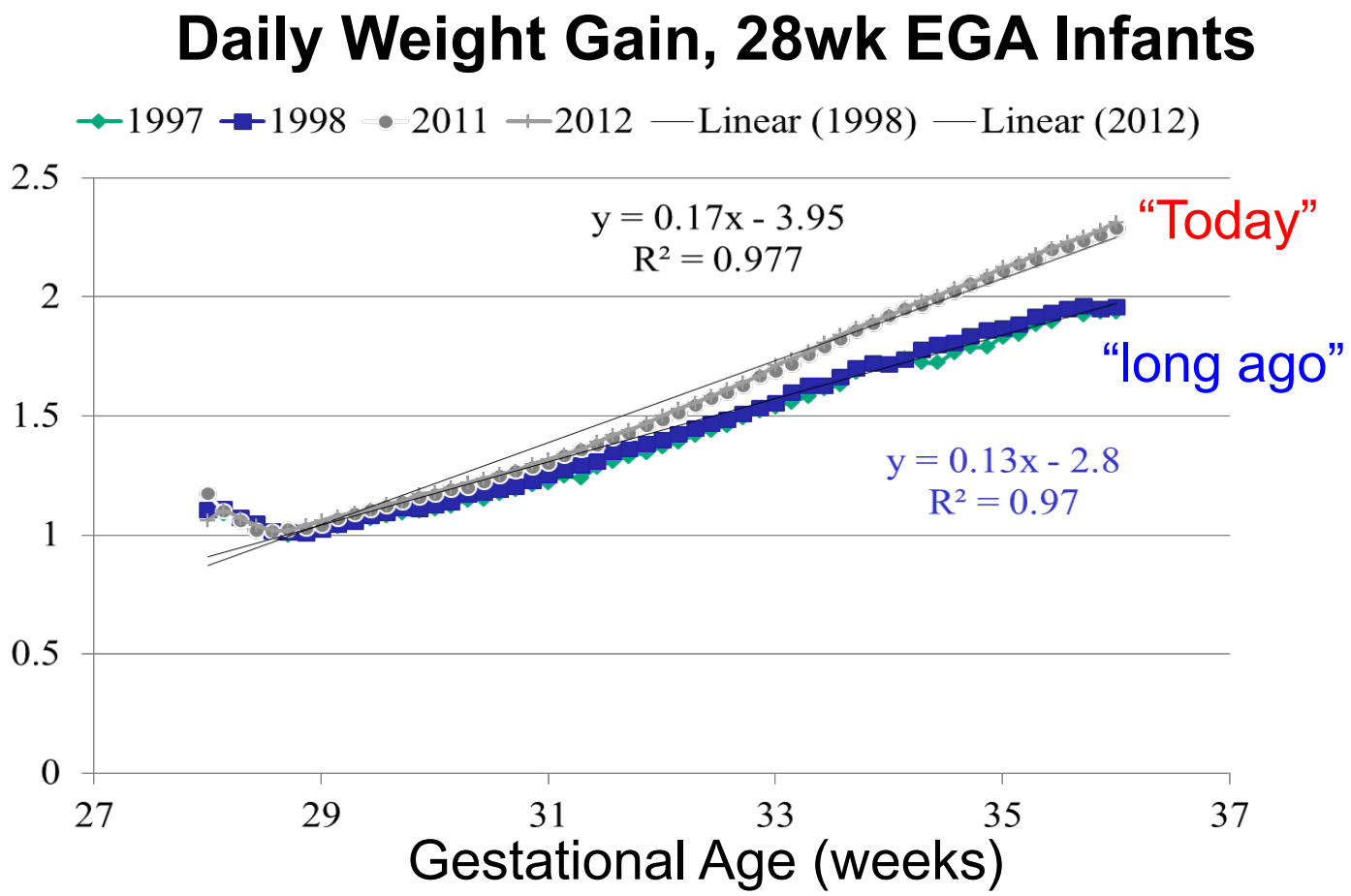
Growth Rates With Varying Protein and Energy Intakes

Preterm infants, birth weight 900 to 1750 grams:
Group 1, dotted bars, 2.24 g/kg/day and 115 kcal/kg/day
Group 2, open bars, 3.6 g/kg/day and 115 kcal/kg/day
Group 3, striped bars, 3.5 g/kg/day and 149 kcal/kg/day



Adapted from Kashyap S, et al. *J Pediatr*. 1986;108:955-963. ©1986, with permission from Elsevier

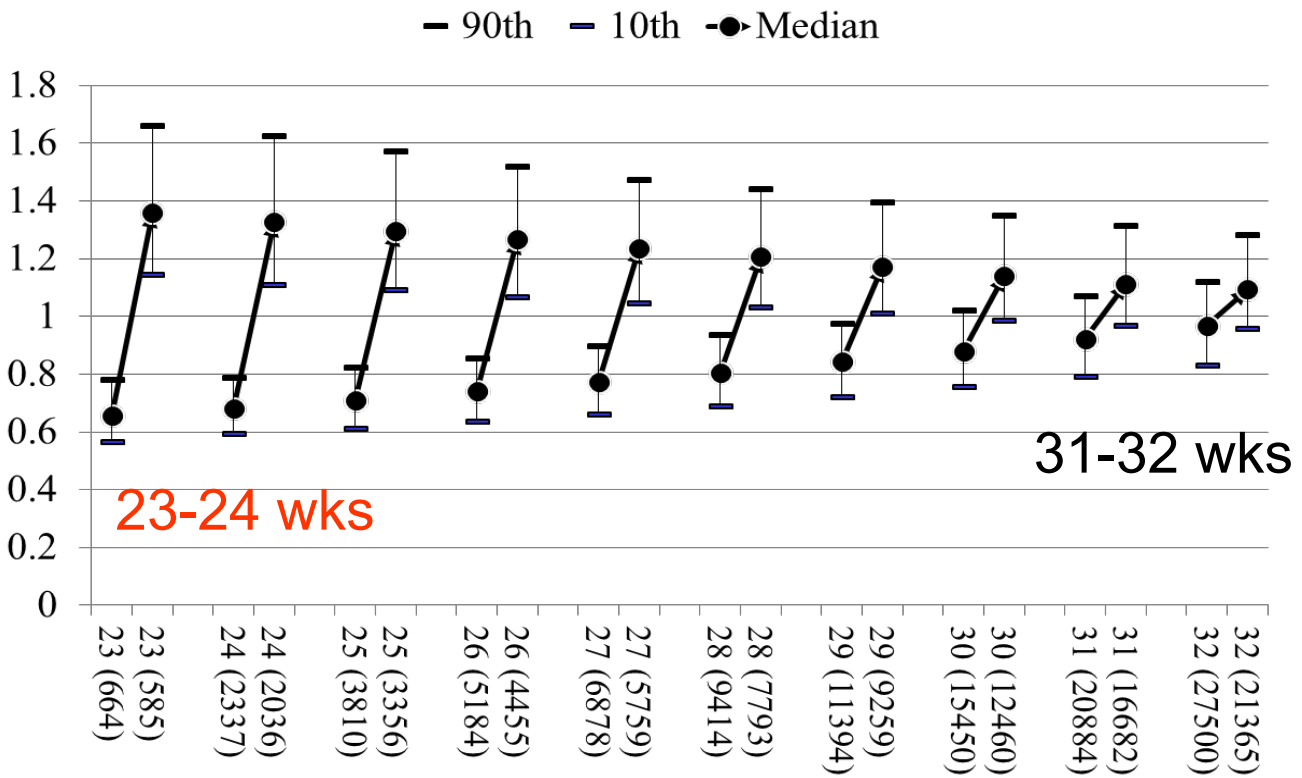
That was long ago. What are we doing today?



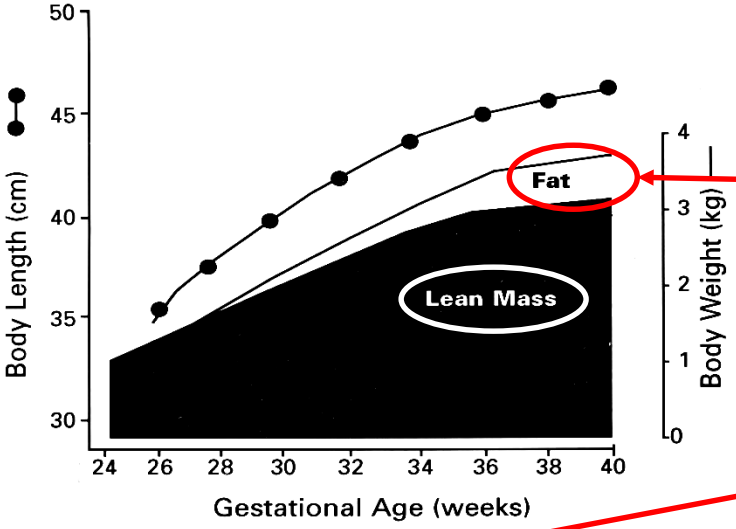
Courtesy Reese Clark Pediatrix University

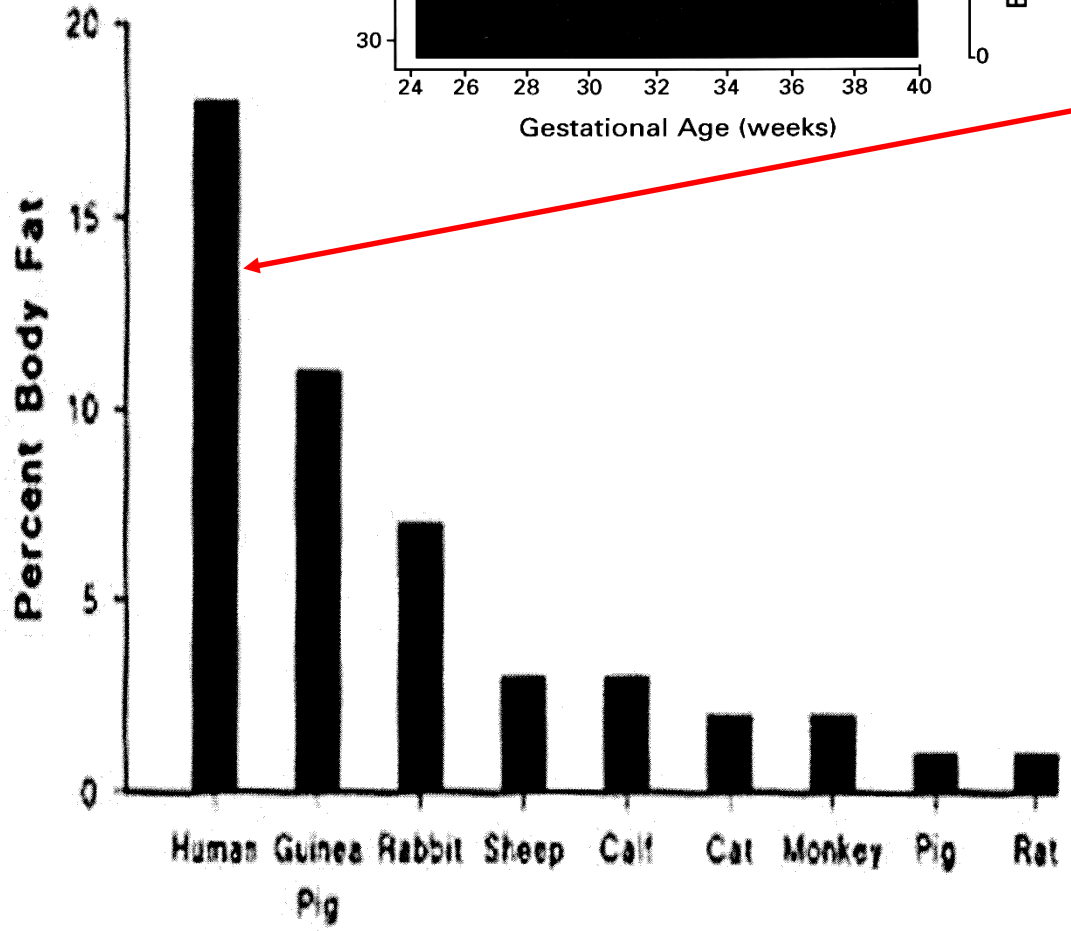
BMI (Weight/Length^2), Birth vs Discharge

The smallest, most preterm infants developed the largest gain in BMI.



Courtesy Reese Clark Pediatrix University





But—
Reminder—
fetal fat accumulation in humans is unique among land mammals.

Maybe this is important to produce in preterm infants?, despite the increasing evidence that fatter fetuses become fatter adults?

Upper: Courtesy William W. Hay, Jr, MD
Lower: Adapted from Widdowson EM, in Assali NS, ed. *Biology of Gestation*, vol 2. New York, NY: Academic Press; 1968:1-48.

Maybe the real problem is not just birth weight, but also rapid postnatal weight gain.

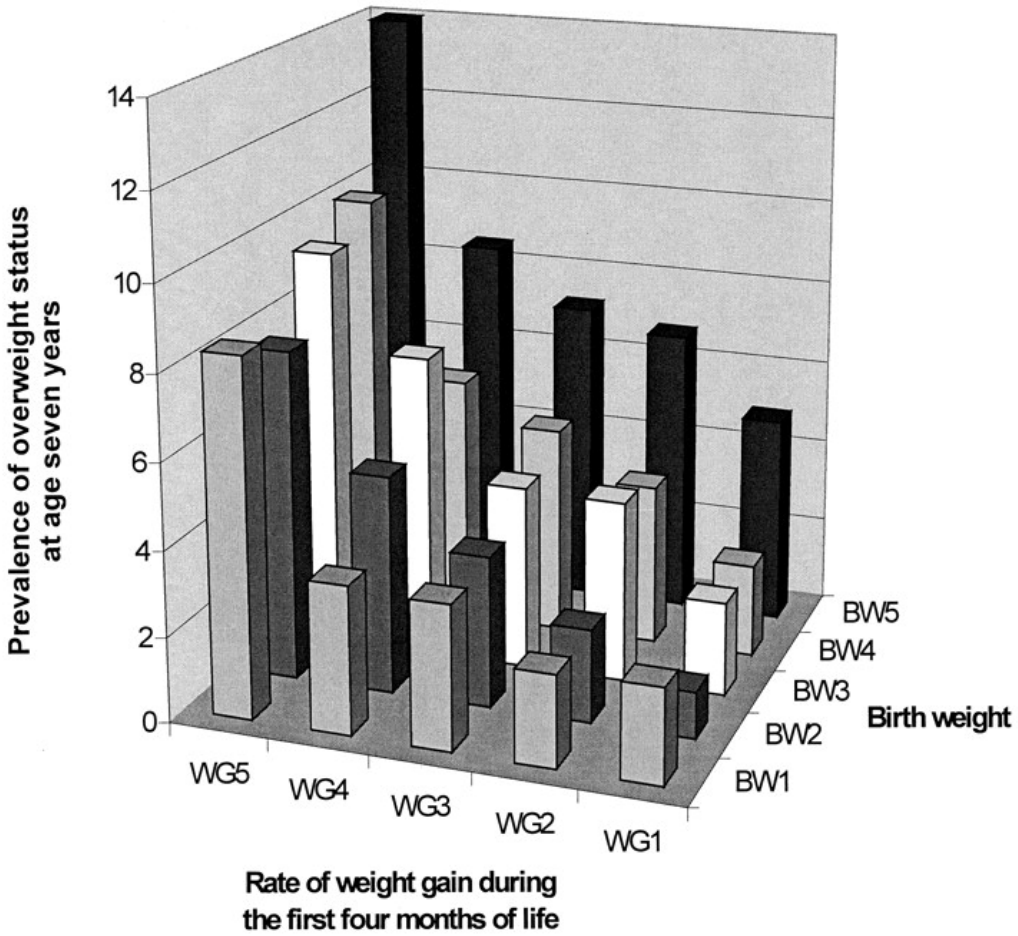


Fig. 1. Prevalence (%) of overweight status at age 7 years by birth weight (kg) quintiles (BWI: 1.30-2.86, BW2: 2.87-3.09, BW3: 3.10-3.32, BW4: 3.33-3.60, BW5: 3.61-5.56) and quintiles of weight gain (g/month) during the first 4 months of life (WG1: -20-670, WG2: 671-780, Wg3: 781-860, WG4: 861-980, WG5: 981-1860) in 19,397 full-term participants.

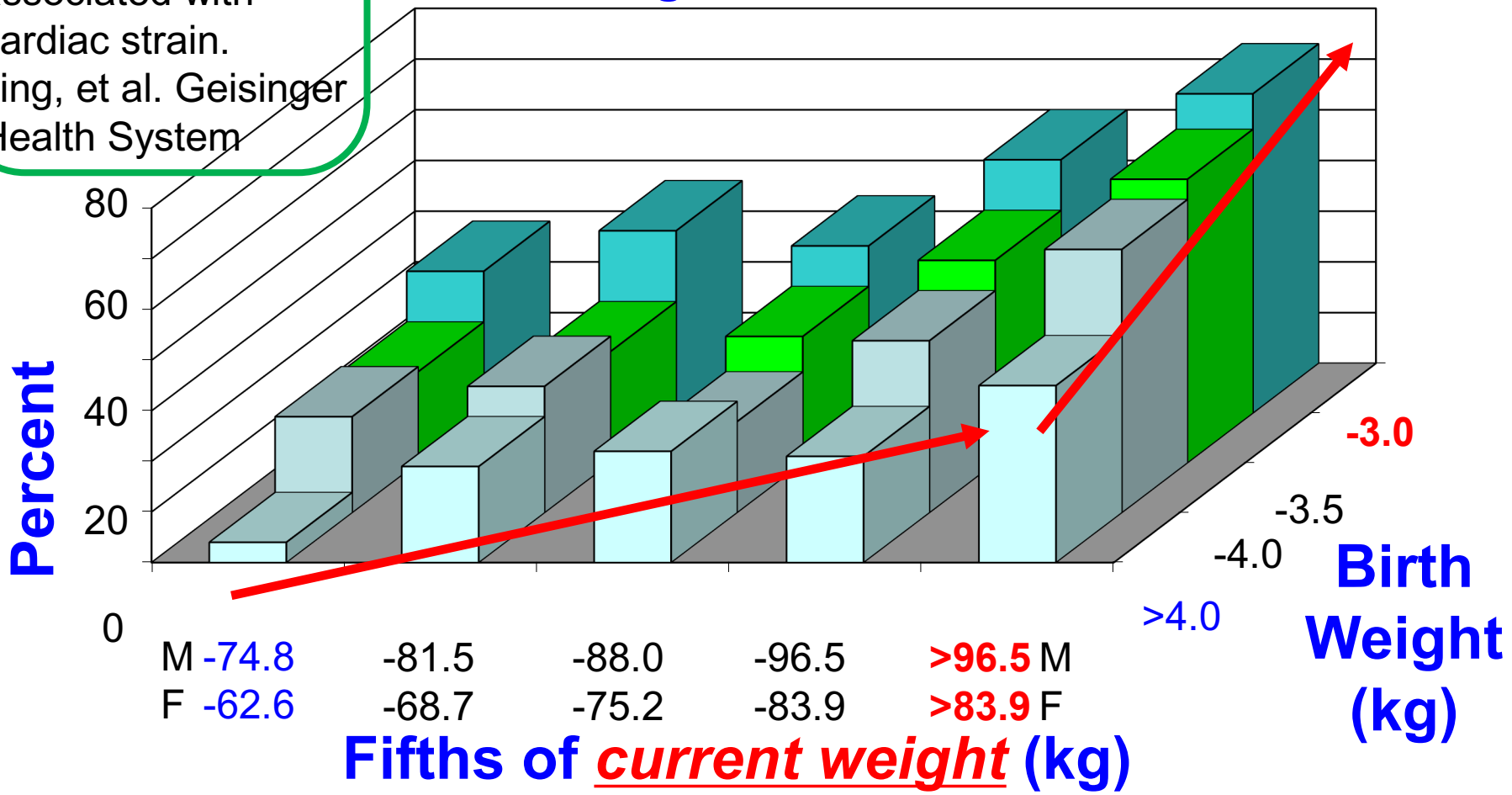
Increasing birth weight

More rapid weight gain

together increase the risk of later life obesity more than either alone.

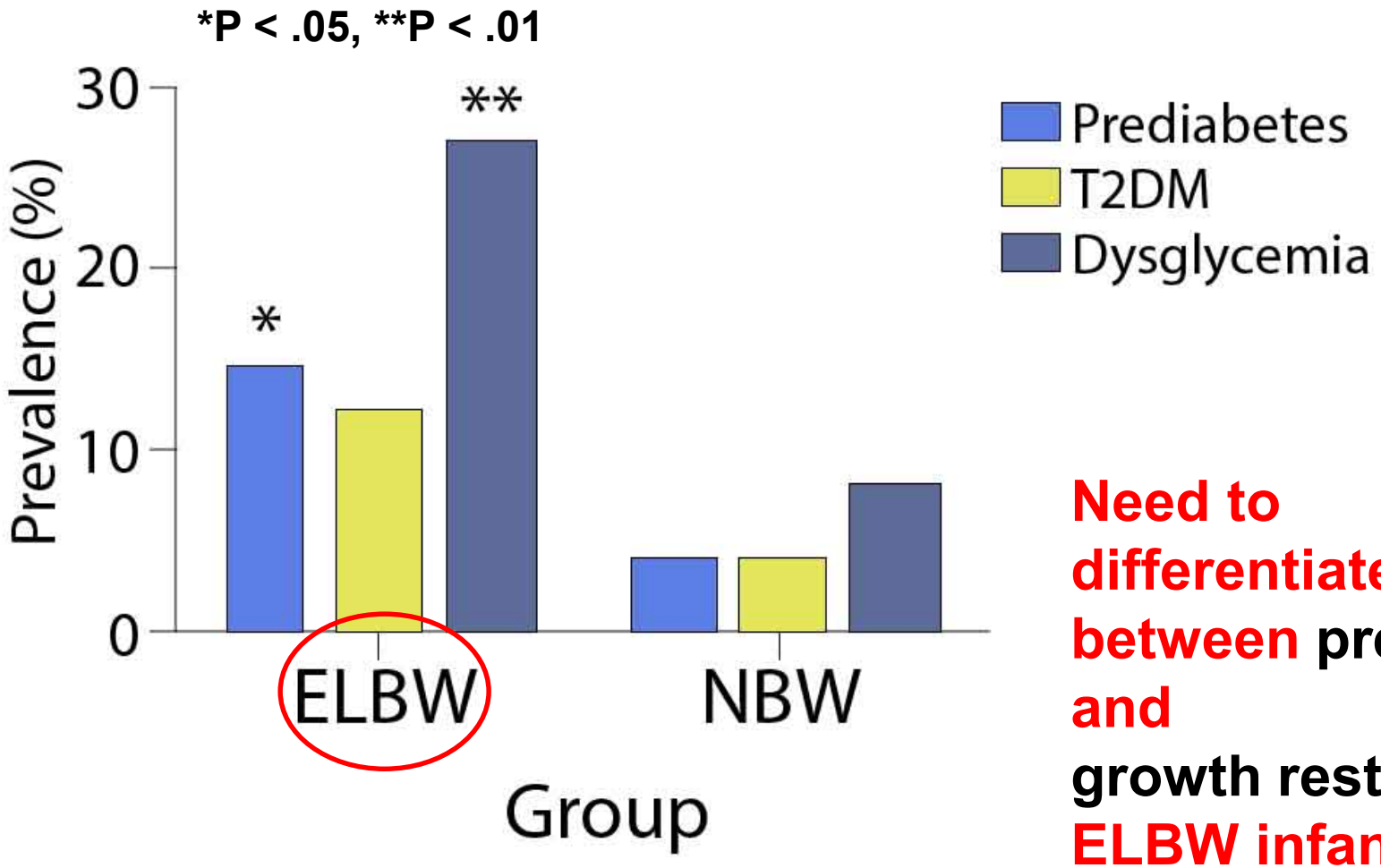
Obese Kids as Young as 8 Show Signs of Heart Disease. MRI scans reveal structural abnormalities associated with cardiac strain. Jing, et al. Geisinger Health System

Increased *weight gain* between 2 and 11 years of age in any child increases the Prevalence of Hypertension (similar data for coronary disease and stroke), as does increasing BW.



Barker JP, et al. *N Engl J Med.* 2005 Oct 27;353(17):1802-9.

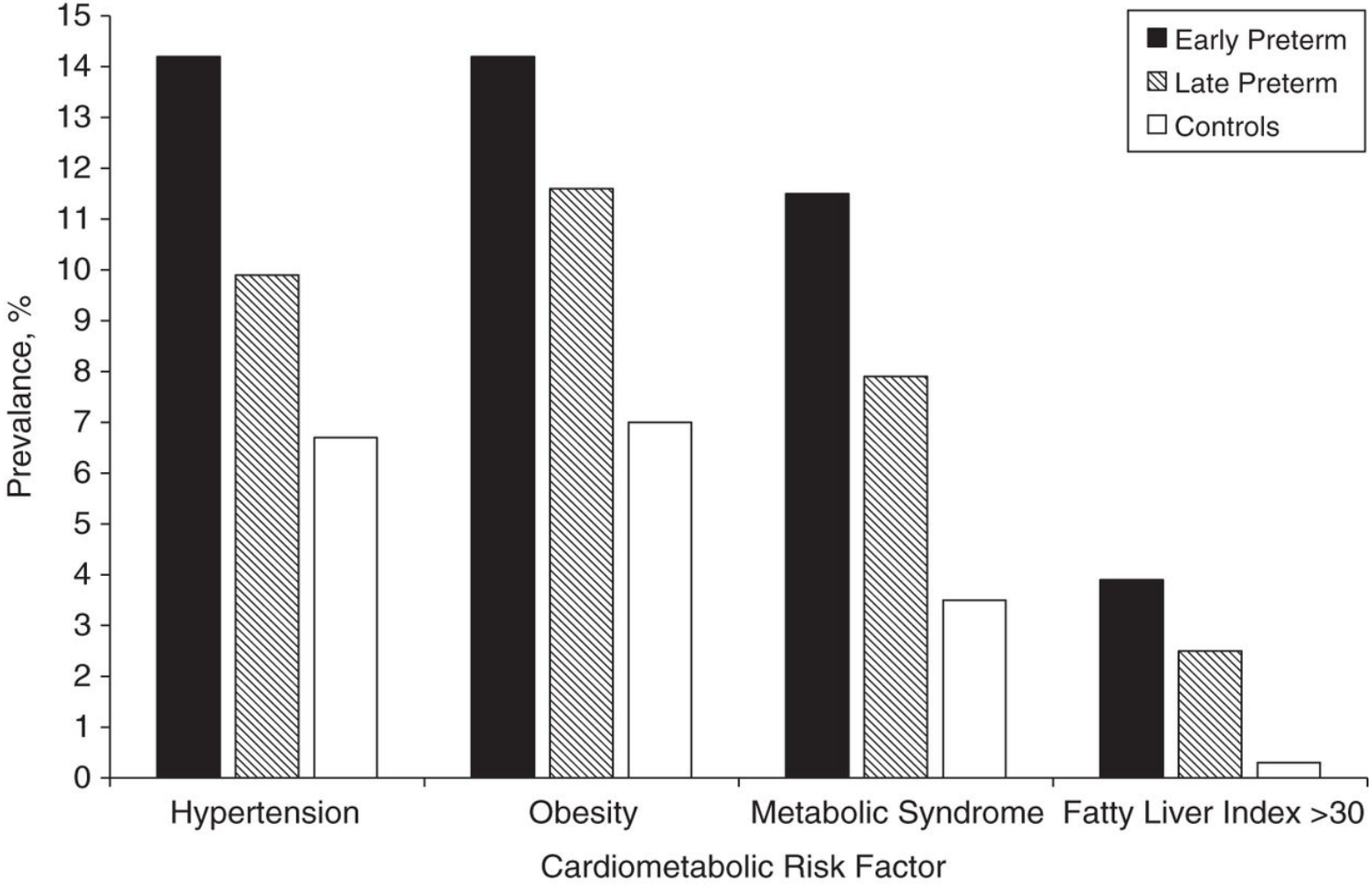
ELBW infants, for whatever reasons, are at increased risk of "dysglycemia" (prediabetes and T2DM)



Need to differentiate between preterm and growth restricted ELBW infants.

Adapted from Morrison KM, et al. *Pediatrics.* 2016;138:e20160515.

Overall, the more preterm the infant at birth, the higher the prevalence of hypertension, obesity, metabolic syndrome, and fatty liver index in adults who were born preterm vs. adults born at term (controls), Northern Finland, 2009–2011.



Marika Sipola-Leppänen et al. *Am J Epidemiol.* 2015;181:861-873

American Journal of EPIDEMIOLOGY

Are there things we could do to prevent rapid gains in weight due to fat mass (higher BMIs) and the inevitable consequences?

But still promote positive neurodevelopmental outcomes?

In humans, breast feeding and human milk appear to be our best bets.

Breastfeeding, considered dichotomously (yes or no), and the Odds Ratio for Later Obesity

- Obesity in the US affects 35%, of adults (~17% of youth aged 2-19).
- Women that were OW/OB prior to conception carried 60% of all US pregnancies (2013).
- Children born to obese mothers have increased likelihood of childhood obesity.
- Exclusive breastfeeding is protective against elevated obesity risk.

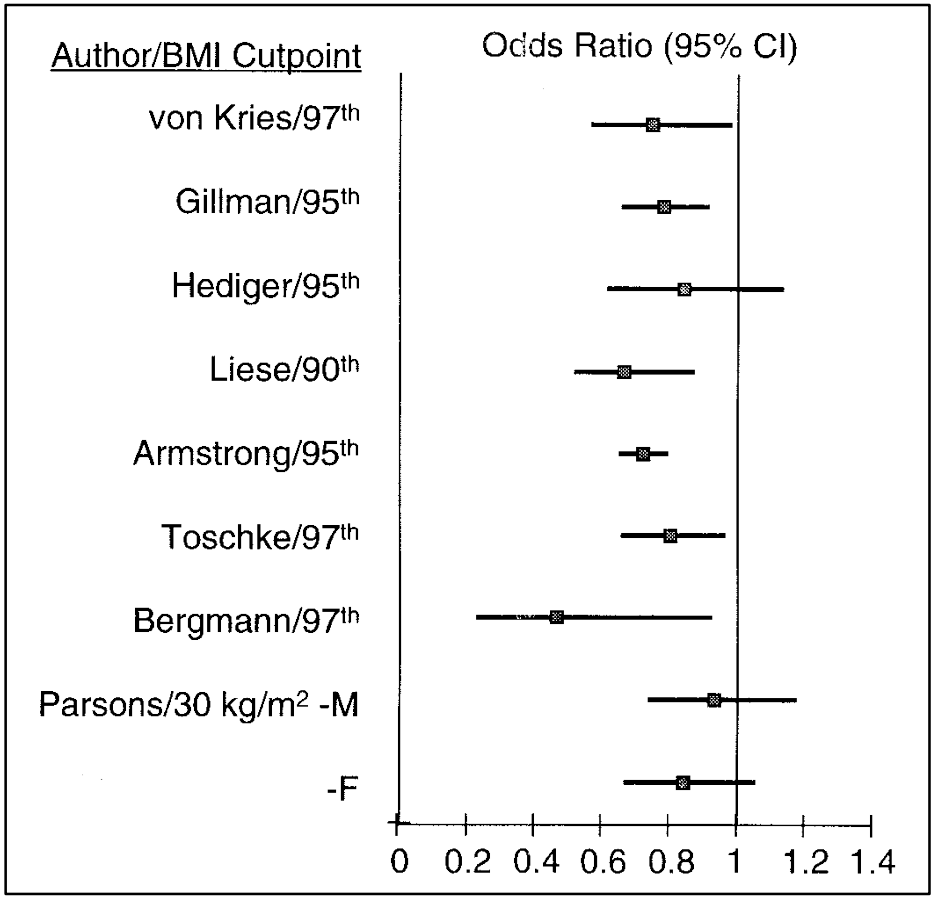
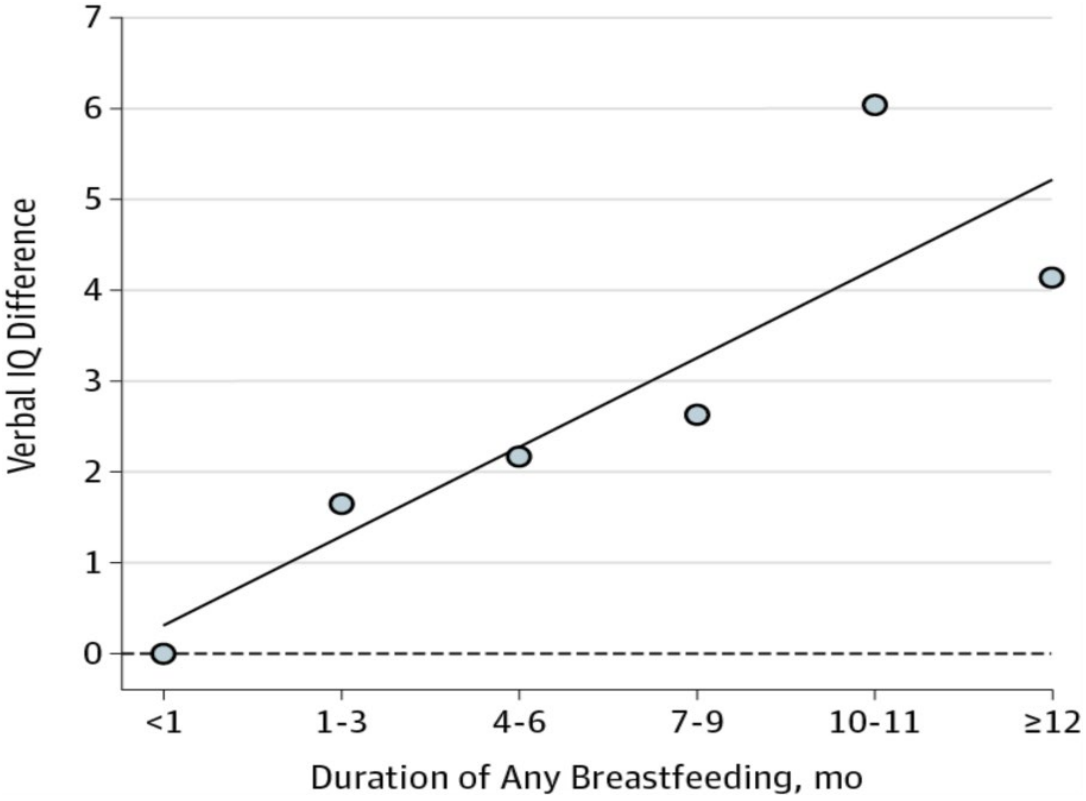


Fig 6. Breastfeeding, considered dichotomously (yes or no), and the OR for later obesity.

The JAMA Network

Improved Childhood Cognition at Ages 3 and 7 in SGA Infants with Prolonged Exclusive Breastfeeding.



Belfort Mandy, et al. ***JAMA Pediatr.*** **2013;167(9):836-844**, and many, many more studies showing improved cognition with breast milk and breast feeding.

But --- how come many exclusively breast fed infants often get fat, some very fat?

But then do not stay fat?

3 month old male,

totally breast fed,

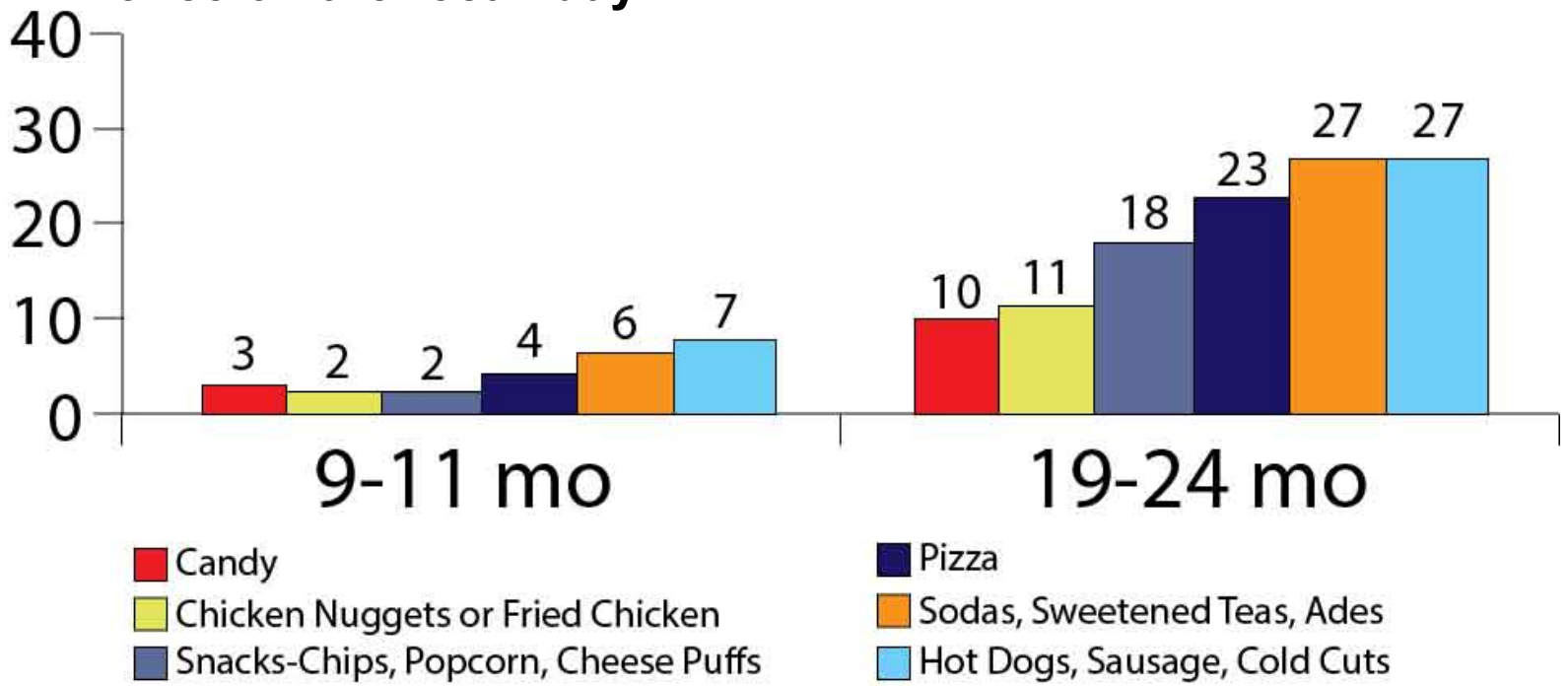
with a clear abundance of subcutaneous fat.

Clearly, more research is needed.

Courtesy William Hay, Jr.

Could it be as simple as breast feeding moms limit the customary diet that children eat, even as early as 2 yrs of age?

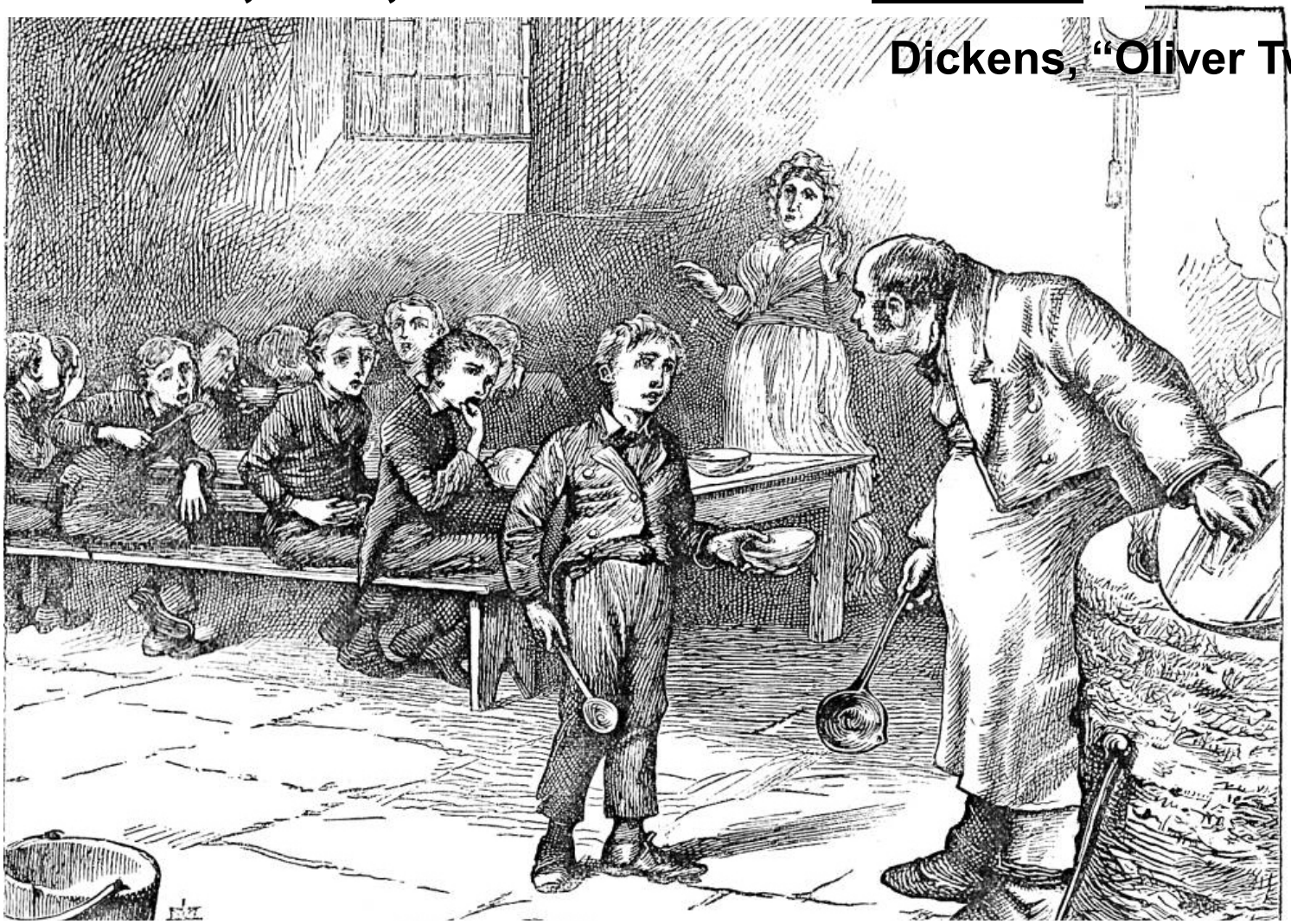
Percentages of infants consuming high-energy foods at least once on the recall day.



Adapted from Lederman SA, et al. *Pediatrics.* 2004;114:1146-1173.

“PLEASE, SIR, I WANT SOME MORE.”

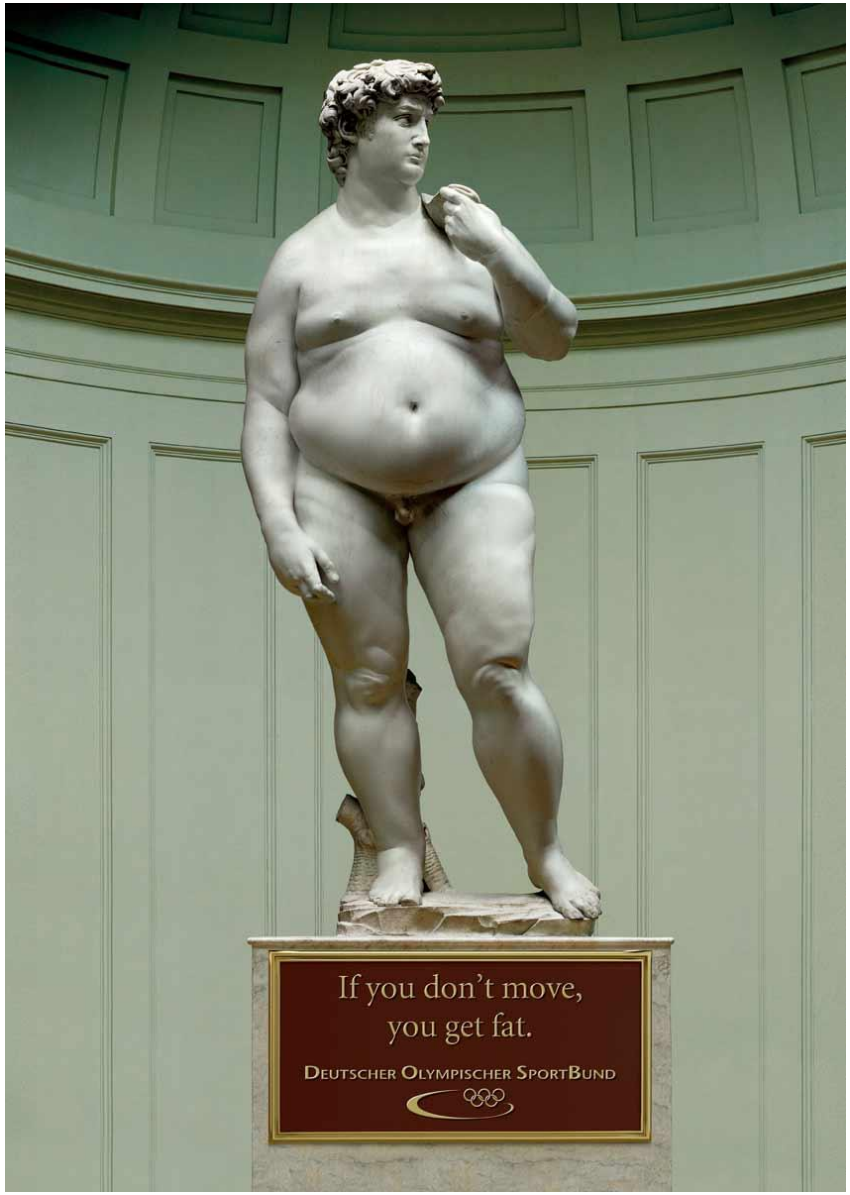
Dickens, “Oliver Twist”



But--what if he had been given more?

Scanned image Philip V. Allingham. "Uncaptioned Headpiece for Chapter One," James Mahoney's interpretation of George Cruikshank's frontispiece for Dickens's The Adventures of Oliver Twist

Maybe this?



“For every individual there is a genetic design which cannot be fulfilled without adequate nutrition.”

Agnes C. Higgins, **1955**

Specific Summary and Recommendations

- Growth outcomes of ELBW infants remain suboptimal, because they are not fed enough, especially of protein.
- In general, preterm infants have been fed excessive energy, which only makes them fatter; but they still lack EFAs (DHA).
- Early protein losses are minimized by providing 3-4 g/kg/d of AAs; less AAs/protein lead to shorter stature and neurological and cognitive deficits.
- Providing ~70 (IV) to~ 90 (enteral) non-protein kcal/kg/d and 3-4 g/kg/d AAs/Protein may approximate fetal protein accretion and growth in reasonably healthy ELBW infants.
- Much research needed to determine optimal AA and energy supplies in sick infants and those who have experienced significant intrauterine and postnatal growth restriction.
- **It does matter, and for a lifetime, what we feed preterm infants at their critical stages of development.**

University of Colorado
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University of Colorado School of Medicine
- Paul Rozance, MD
- Laura Brown, MD
- Stephanie Wesolowski, PhD
- Jed Friedman, PhD
- Patti Thureen, MD (deceased)
- Kendra Hendrickson, RD (UCH)
- Many wonderful fellows and lab personnel

The University of Arizona
- Sean Limesand, PhD

University of Aberdeen, (Scotland)
- Jacqueline Wallace, PhD

Funding
- NICHD K12 and T32 training grants (Hay, PI and PD)
- NCATS CTSA (Hay, Director for Child and Maternal Health Pilot Grant Program and the Early Life Exposures Program)
- NIH grants for collaborators: KO8/RO1 (Rozance), KO1/RO1 (Wesolowski), K12/RO1 (Brown), KO1/RO1 (Limesand), and others (Friedman)